FRÉQUENCE MÉDICALE ONCOLOGIE

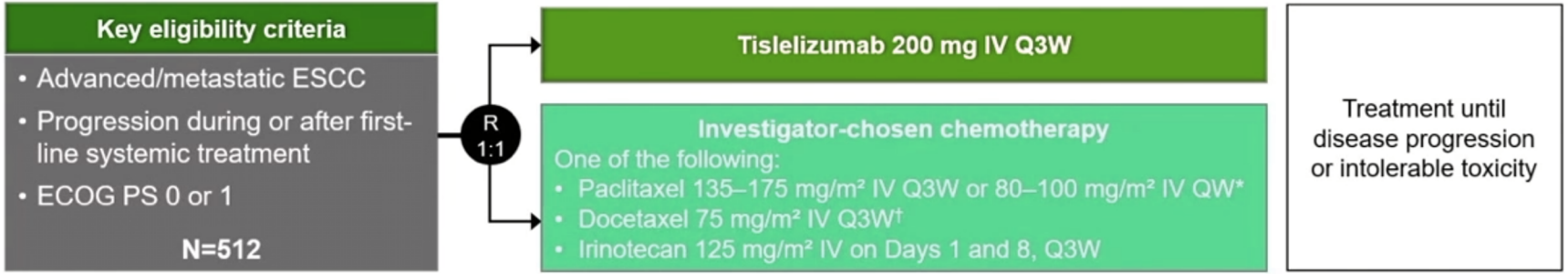
2021

FRÉQUENCE MÉDICALE ONCOLOGIE

Post ESMO GI 2021

Cancers Oeso-gastriques

RATIONAL-302: Study Design



Stratification factors

- Region (Asia [excluding Japan] vs Japan vs Europe/North America)
- ECOG PS (0 vs 1)
- Chemotherapy option (paclitaxel vs docetaxel vs irinotecan)

Endpoints

- Primary endpoint: OS in all randomized patients (ITT population)
- Key secondary endpoint: OS in patients with vCPS ≥10%‡
- Other secondary endpoints: PFS, ORR, DOR, HRQoL, and safety

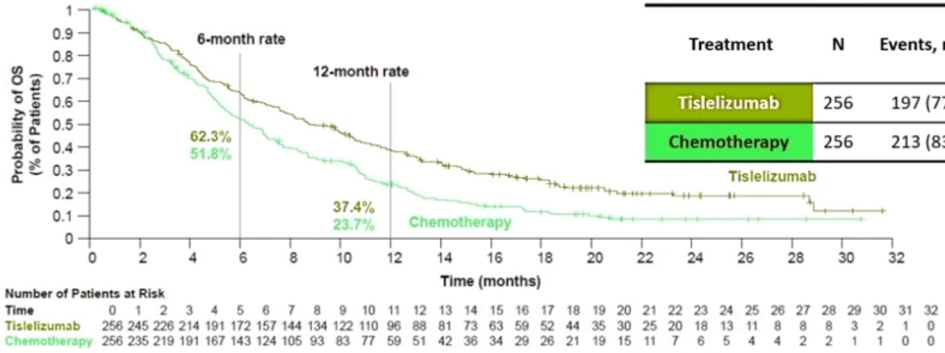
The study required ~400 death events to achieve 82% power to detect a HR of 0.75 at 0.025 significance level (1-sided) for the primary endpoint of OS in all randomized patients (ITT analysis set)

Demographics and baseline patient characteristics

		Overall Population		EU/NA Subgroup	
		Tislelizumab (n=256)	Chemotherapy (n=256)	Tislelizumab (n=55)	Chemotherapy (n=53)
Median Age (range), years		62 (40–86)	63 (35–81)	65 (41–86)	65 (35–80)
Male, n (%)		217 (84.8)	215 (84.0)	37 (67.3)	36 (67.9)
Region	Asia	201 (78.5)	203 (79.3)	0.0	0.0
	Europe/North America	55 (21.5)	53 (20.7)	55 (100)	53 (100)
Race, n (%)	Asian	201 (78.5)	207 (80.9)	0.0	4 (7.5)
	White/Caucasian	53 (20.7)	44 (17.2)	53 (96.4)	44 (83.0)
	Black/African American	0.0	2 (0.8)	0.0	2 (3.8)
	Other*	2 (0.8)	3 (1.2)	2 (3.6)	3 (5.7)
ECOG PS, n (%)	0	66 (25.8)	60 (23.4)	23 (41.8)	18 (34.0)
	1	190 (74.2)	196 (76.6)	32 (58.2)	35 (66.0)
PD-L1 Status†, n (%)	vCPS ≥10%	89 (34.8)	68 (26.6)	22 (40.0)	10 (18.9)
	vCPS <10%	116 (45.3)	140 (54.7)	27 (49.1)	37 (69.8)
	Unknown	51 (19.9)	48 (18.8)	6 (10.9)	6 (11.3)
Disease Status at Baseline, n (%)	Locally advanced	5 (2.0)	20 (7.8)	2 (3.6)	6 (11.3)
	Metastatic	251 (98.0)	236 (92.2)	53 (96.4)	47 (88.7)
Prior Therapies, n (%)	Surgery	94 (36.7)	99 (38.7)	9 (16.4)	10 (18.9)
	Radiotherapy	169 (66.0)	163 (63.7)	34 (61.8)	34 (64.2)
	Platinum-based chemotherapy	249 (97.3)	252 (98.4)	54 (98.2)	53 (100.0)

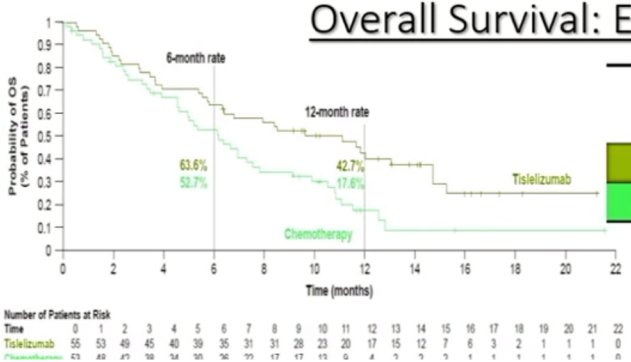
Rationale-302: OS

Overall Survival: Overall Population



Treatment	N	Events, n (%)	Median OS (95% CI), months*	Tislelizumab vs Chemotherapy	
				HR (95% CI)†	*P*-value
Tislelizumab	256	197 (77.0)	8.6 (7.5–10.4)	0.70 (0.57–0.85)	0.0001‡
Chemotherapy	256	213 (83.2)	6.3 (5.3–7.0)		

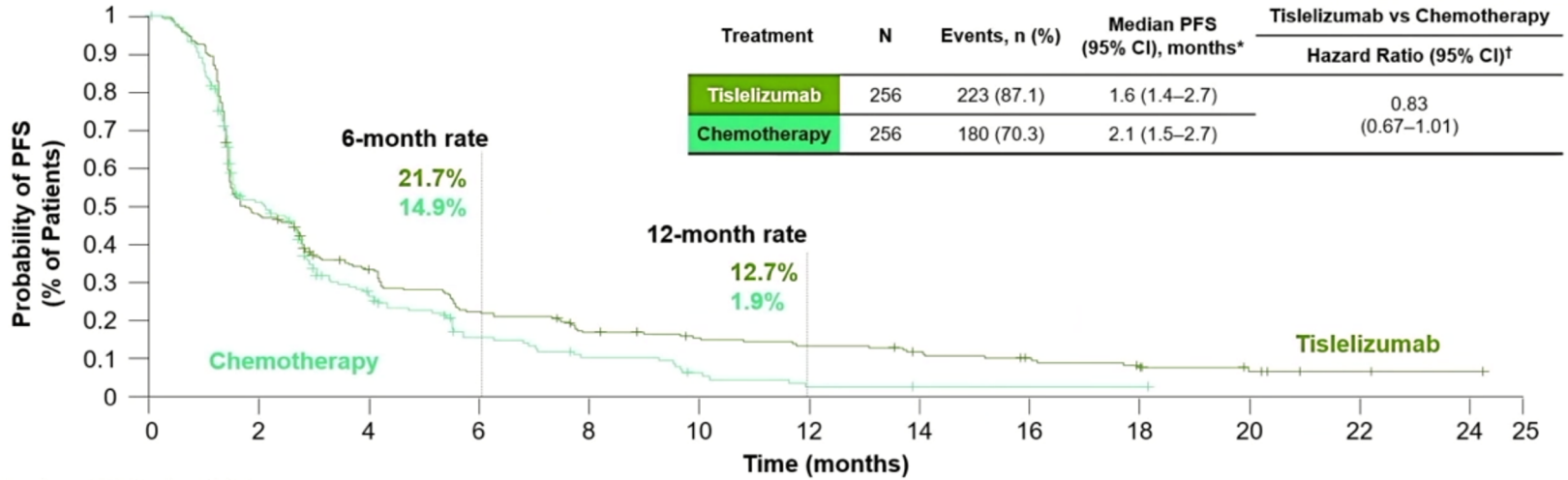
Overall Survival: EU/NA Subgroup



Treatment	N	Events, n (%)	Median OS (95% CI), months*	Tislelizumab vs Chemotherapy
				Hazard Ratio (95% CI)†
Tislelizumab	55	35 (63.6)	11.2 (5.9–14.8)	0.55 (0.35–0.87)
Chemotherapy	53	42 (79.2)	6.3 (4.6–7.7)	

PFS: Overall and EU/NA populations

Treatment	N	Events, n (%)	Median PFS (95% CI), months*	Tislelizumab vs Chemotherapy Hazard Ratio (95% CI)†
Tislelizumab	256	223 (87.1)	1.6 (1.4–2.7)	0.83 (0.67–1.01)
Chemotherapy	256	180 (70.3)	2.1 (1.5–2.7)	



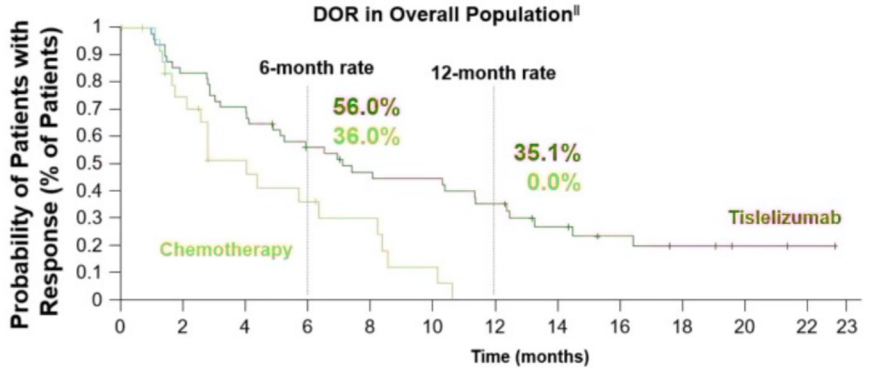
Number of Patients at Risk

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Tislelizumab	256	233	119	85	74	62	49	46	35	32	28	27	25	25	20	18	15	13	9	8	6	3	3	2	2	0
Chemotherapy	256	184	98	57	42	33	20	16	12	12	6	4	2	2	1	1	1	1	1	0	0	0	0	0	0	0

In the EU/NA subgroup, there was no meaningful difference in PFS between the two arms (HR=0.97, 95% CI: 0.64–1.47)

ORR and DOR: Overall Population

	Tislelizumab (n=256)	Chemotherapy (n=256)
ORR, n	52	**25**
% (95% CI)*	20.3 (15.6–25.8)	9.8 (6.4–14.1)
Odds Ratio for ORR, (95% CI)†	2.4 (1.4–4.0)	
Best Overall Response, n (%)		
Complete Response	5 (2.0)	1 (0.4)
Partial Response	47 (18.4)	24 (9.4)
Stable Disease	68 (26.6)	82 (32.0)
Progressive Disease	116 (45.3)	86 (33.6)
DOR§		
Median (95% CI), months	7.1 (4.1–11.3)	4.0 (2.1–8.2)
Pts with Ongoing Response, n (%)	10 (19.2)	0 (0.0)



Number of Patients at Risk

Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Tislelizumab	52	47	40	36	34	29	25	22	20	19	19	17	15	11	9	7	6	5	4	3	2	2	1	0
Chemotherapy	25	24	17	10	10	8	7	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0

Data cut-off date: 01 Dec 2020. Overall population was stratified according to region, ECOG performance score, and chemotherapy treatment. Data are investigator assessed per RECIST v1.1.
*Two-sided 95% CI was calculated using Clopper-Pearson method. †Calculated using the Cochran-Mantel-Haenszel Chi-square test. ‡Including those with no post-baseline assessment or an unevaluable post-baseline assessment. §Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. DOR analysis included patients with objective response (complete or partial response). ¶Hazard ratio was based on unstratified Cox regression model including treatment as covariate. ‖DOR rates (cumulative probability of DOR) were estimated by Kaplan-Meier method with 95% CIs estimated using Greenwood's formula

CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ORR, overall response rate; pts, patients; RECIST, response evaluation criteria in solid tumors

Summary of adverse events

	Overall Population		EU/NA Subgroup	
	Tislelizumab (n=255)	Chemotherapy (n=240)	Tislelizumab (n=54)	Chemotherapy (n=49)
Patients with ≥1 TEAE	**244 (95.7)**	**236 (98.3)**	**52 (96.3)**	**47 (95.9)**
Grade 3–5	118 (46.3)	163 (67.9)	30 (55.6)	35 (71.4)
Serious AEs	105 (41.2)	105 (43.8)	21 (38.9)	23 (46.9)
Leading to death*	14 (5.5)	14 (5.8)	3 (5.6)	5 (10.2)
Leading to treatment discontinuation	49 (19.2)	64 (26.7)	8 (14.8)	15 (30.6)
Most Common (Incidence ≥20%) TRAEs				
Anemia	28 (11.0)	83 (34.6)	2 (3.7)	13 (26.5)
Decreased appetite	16 (6.3)	75 (31.3)	5 (9.3)	12 (24.5)
Diarrhea	14 (5.5)	66 (27.5)	7 (13.0)	16 (32.7)
Nausea	7 (2.7)	66 (27.5)	3 (5.6)	12 (24.5)
White blood cell count decreased	5 (2.0)	98 (40.8)	0	2 (4.1)
Neutrophil count decreased	3 (1.2)	94 (39.2)	0	5 (10.2)

Phase 3 studies with Anti-PD-1 Antibody in 2nd line ESCC

	RATIONALE-302 (Tislelizumab)	ATTRACTION-3 (Nivolumab)	KEYNOTE-181 (Pembrolizumab)
Number of Patients	512	419	628
Tumor Histopathology	SCC	SCC	64% SCC
% of PD-L1 Expression	**31% (≥ vCPS# 10)**	**48% (≥ TPS 1)**	**35% (≥ CPS 10)**
Control Arm	PTX, DTX, or IRI	PTX or DTX	PTX, DTX, or IRI
Geography/Race	79% in Asia	96% in Asia	39% in Asia
mOS in ESCC (Δ of mOS from control)	8.6 m (Δ; 2.3 m)	10.9 m (Δ; 2.5 m)	8.2 m (Δ; 1.1 m)
HR in OS of ESCC	0.70	0.77	0.78
OS in ESCC with PD-L1 positive (Δ from control)	10.3 m (Δ; 3.5 m)	10.9 m (Δ; 2.8 m)	10.3 m (Δ; 3.6 m)
mPFS in ESCC	1.6 m	1.7 m	2,2 m
ORR in ESCC	20.3%	19%	16.7%
mDOR	7.1 m	6.9 m	8.5 m

LBA-5: Phase Ib study of anti-TIGIT antibody tiragolumab in combination with atezolizumab in patients with metastatic oesophageal cancer

LBA-5: Phase Ib study of the anti-TIGIT antibody tiragolumab in combination with atezolizumab in patients with metastatic esophageal cancer

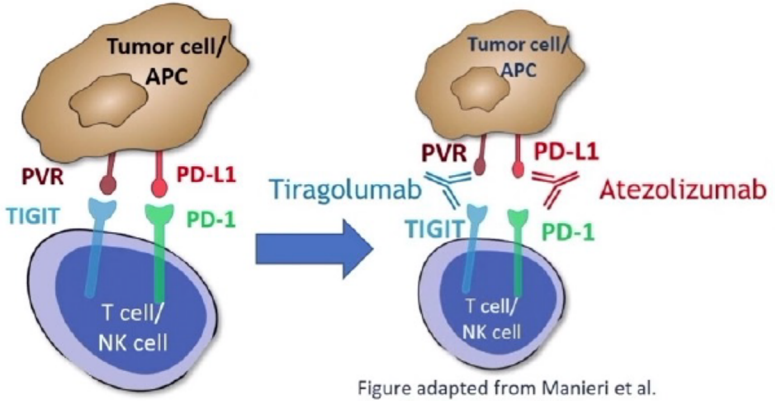
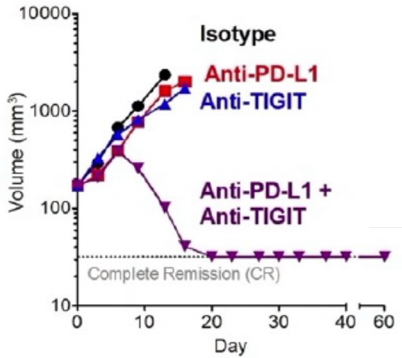


Figure adapted from Manieri et al. *Trends Immunology* 2017



[1] Johnston et al. *Cancer Cell* 2014

TIGIT is a novel inhibitory immune checkpoint present on activated T cells and NK cells in multiple cancers.

In preclinical models, combination treatment with anti-TIGIT and anti-PD-L1 antibodies synagistically improves tumor control and prolongs survival in mice.

Tiragolumab could restore the anti-tumor response and may amplify the activity of anti-PD-L1/PD-1 antibodies.

TIGIT; T cell immunoreceptor with Ig and ITIM domains

Objective:

- To determine the preliminary safety, tolerability, and anti-tumor activity of tiragolumab 600 mg IV Q3W and atezolizumab 1200 mg IV Q3W in metastatic esophageal cancer

Eligibility:

- Metastatic esophageal cancer of any histology
- No limit on prior lines of therapy
- No prior treatment with immunotherapy
- Any PD-L1 status

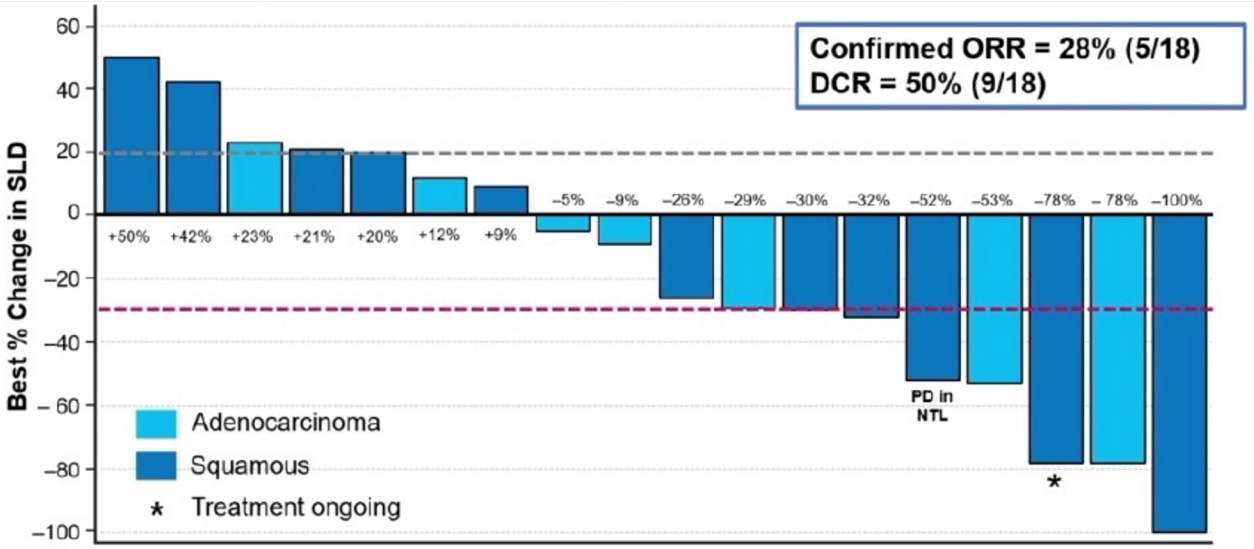
Baseline characteristics and patient disposition

Characteristic, n (%)		Tiragolumab + Atezolizumab (n=21)
Age in years, median (range)		62 (50–77)
Male		18 (86%)
ECOG Performance Status 1		16 (76%)
Race	White	9 (43%)
	Asian	7 (33%)
	Other	5 (24%)
Prior cancer therapies[a]	1	6 (29%)
	2	8 (38%)
	≥3	7 (33%)
Histopathologic subtype	Squamous	13 (62%)
	Adenocarcinoma	8 (38%)
PD-L1 status (VENTANA PD-L1 SP142 assay)	TC or IC ≥5%	5 (24%)

Disposition, n (%)	Tiragolumab + Atezolizumab (n=21)
Ongoing	1 (5%)
Discontinued study	20 (95%)
Progression/death	15 (71%)
Withdrawal	3 (14%)
Lost to follow-up	2 (10%)

[a]Includes neoadjuvant and/or adjuvant therapy
ECOG; Eastern Cooperative Oncology Group; IC, immune cell; TC, tumor cell
Note: This expansion cohort began enrolment in October 2017. Clinical cutoff date: 8 April 2021

Anti-tumor activity: waterfall plot



Prior lines of systemic therapy	2	2	2	3	2	1	3	4	3	1	8	2	1	2	2	4	2	1
PD-L1 TC or IC <5%												n/e						
PD-L1 TC or IC ≥5%												n/e						

Three patients discontinued for clinical progression prior to first scan (bowel perforation, pericardial effusion related to disease, and GI bleed)
VENTANA SP142 PD-L1 assay used to determine PD-L1 expression
DCR, disease control rate; IC, immune cell; NTL, non-target lesion; ORR, overall response rate; PD, progression of disease;
SLD, sum of longest diameters; TC, tumor cell
Clinical cutoff date: 8 April 2021

Safety summary of adverse events

Patients with ≥1 adverse event (AE), n (%)	Tiragolumab + Atezolizumab (n=21)
Any-cause AE	21 (100%)
Grade 3–4 AEs (all cause)	14 (67%)
Treatment-related Grade 3–4 AEs[a]	1 (5%)
Serious AE	15 (71%)
AE leading to any treatment interruption	8 (38%)
AE leading to any treatment discontinuation[b]	1 (5%)
All treatment-related AEs	14 (67%)
Grade 1	7 (33%)
Grade 2	6 (29%)
Grade 3[a]	1 (5%)
All immune-mediated AEs	12 (57%)
Grade 1	5 (24%)
Grade 2	4 (19%)
Grade 3[c]	3 (14%)

[a]One patient had a related Grade 3 AE of lymphocyte count decreased
[b]One patient discontinued treatment for Grade 5 upper airway obstruction not related to study drugs
[c]Grade 3 immune-mediated AEs included amylase increased (n=2) and transaminase increased (n=1)
Clinical cutoff date: 8 April 2021

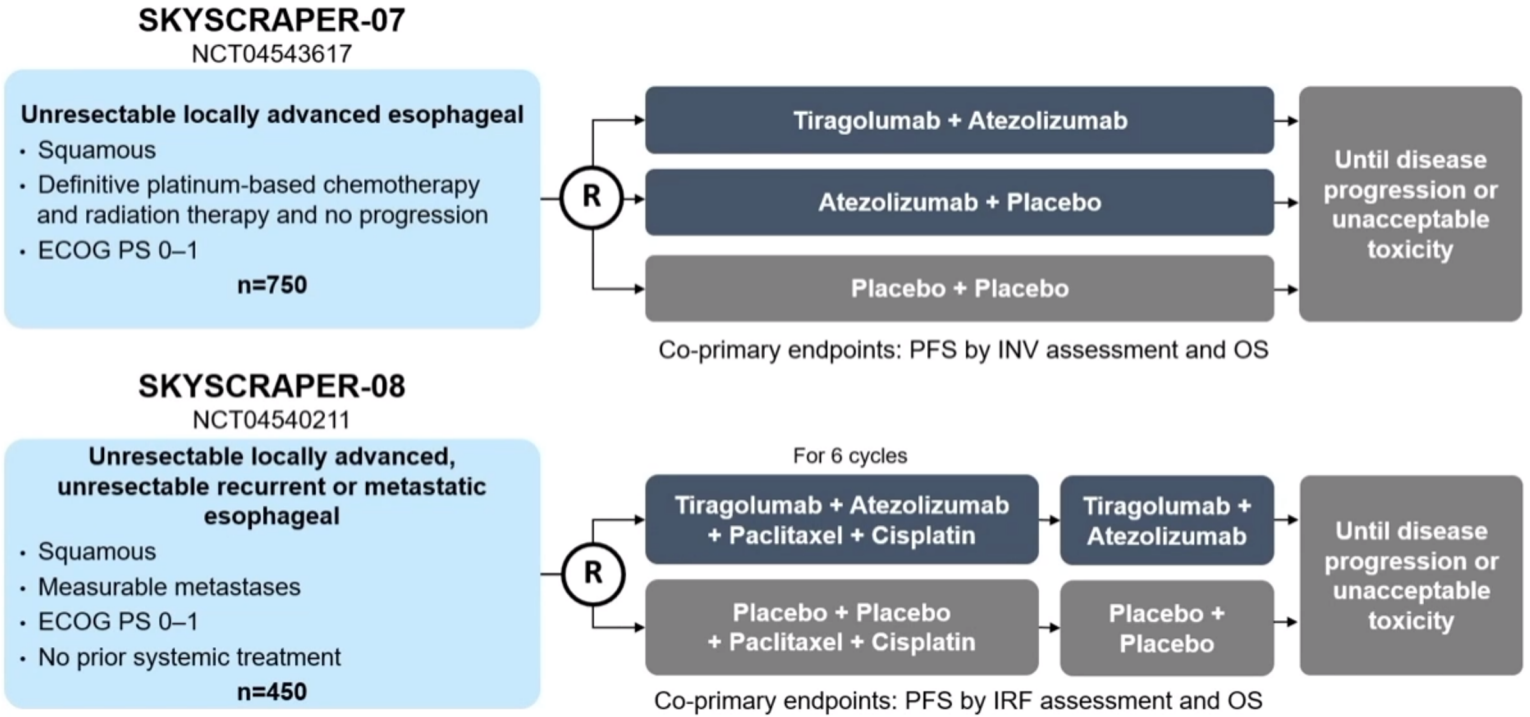
Most common Aes and all immune-mediated AEs

All adverse events (AE) ≥10%	Tiragolumab + Atezolizumab (n=21)
Anaemia	5 (24%)
Decreased appetite	4 (19%)
Cough	4 (19%)
Aspartate aminotransferase increase	4 (19%)
Amylase increase	4 (19%)
Dysphagia	3 (14%)
Pyrexia	3 (14%)
Pruritus	3 (14%)
Rash	3 (14%)
Alanine aminotransferase increased	3 (14%)

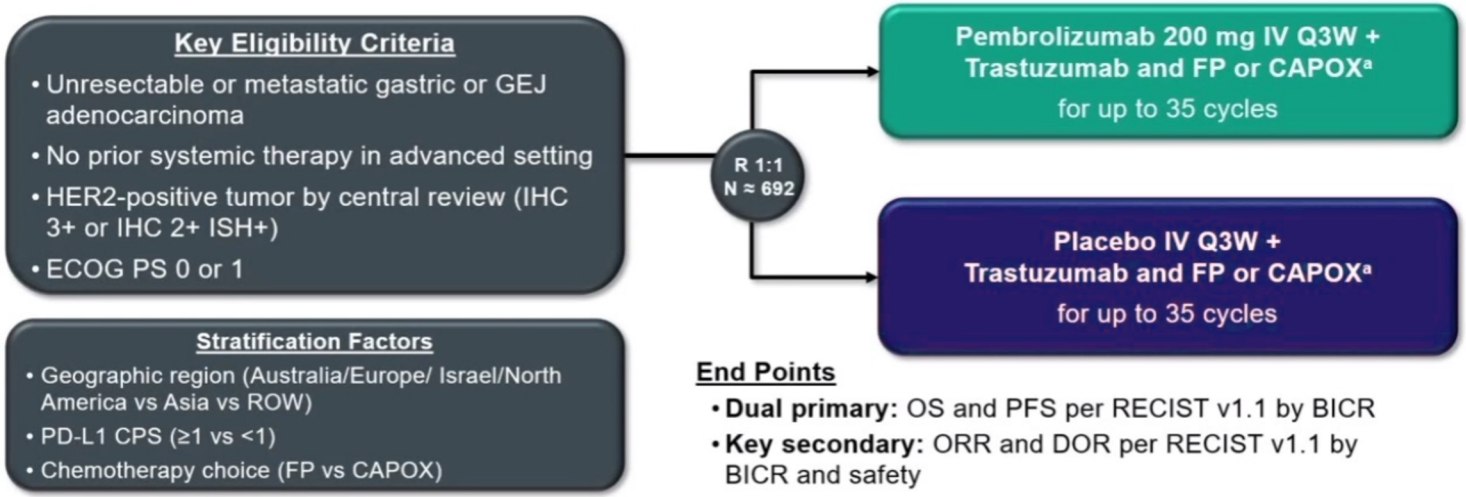
All immune-mediated AEs (imAEs)[a]	Tiragolumab + Atezolizumab (n=21)
Rash	8 (38%)
Hepatitis (laboratory abnormalities)[b]	5 (24%)
Pancreatitis (laboratory abnormalities)[b]	4 (19%)
Diabetes	1 (5%)
Hyperthyroidism	1 (5%)
Hypophysitis	1 (5%)
Hypothyroidism	1 (5%)

[a]imAEs reported by medical concepts; [b]All cases only laboratory abnormalities and not confirmed diagnosis (no clinical symptoms)
Clinical cutoff date: 8 April 2021

Ongoing tiragolumab studies in esophageal cancer



KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study



Protocol-Specified First Interim Analysis (IA1), Data cutoff date: June 17, 2020

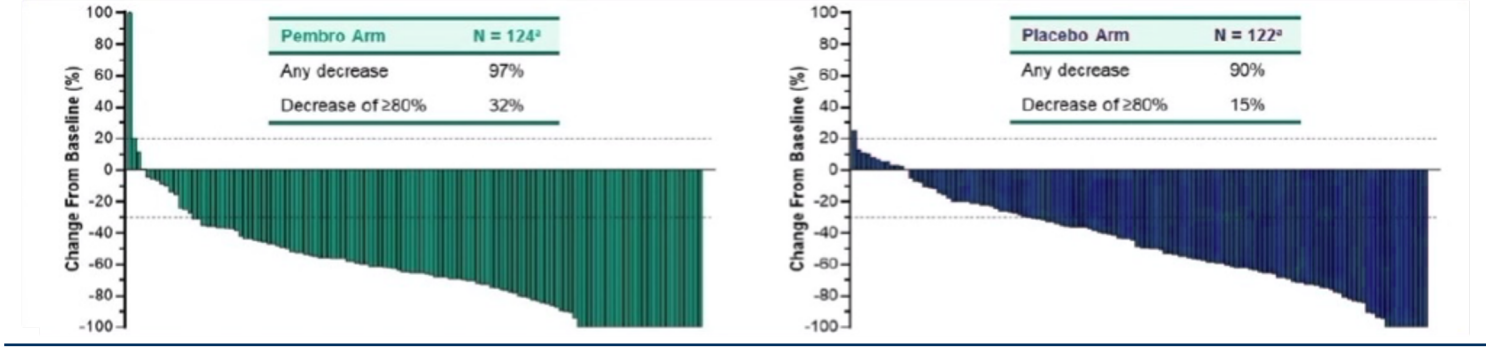
- *Timing: when first 260 participants enrolled had ≥8.5 mo of follow-up*
- *Objective: to assess whether adding pembrolizumab to trastuzumab and chemotherapy significantly improves ORR*
- *Superiority boundary: P = 0.002 (one-sided)*
- *Efficacy: first 264 participants enrolled*
- *Safety: all enrolled participants who received ≥1 dose of study medication (N=433)*

Baseline characteristics at IA1

	Efficacy Population		ITT Population	
	Pembro Arm (N = 133)	Placebo Arm (N = 131)	Pembro Arm (N = 217)	Placebo Arm (N = 217)
Age, median (range)	62 y (19-84)	61 y (32-83)	62 y (19-84)	63 y (32-83)
Male sex	84%	79%	82%	80%
Region of enrollment				
Aus/Eur/Isr/NAm	31%	34%	31%	31%
Asia	30%	30%	35%	35%
ROW	39%	37%	34%	35%
ECOG PS 1	51%	55%	53%	59%
Primary location of stomach	72%	68%	71%	65%
Histologic subtype				
Diffuse	21%	20%	22%	18%
Intestinal	61%	48%	54%	47%
Indeterminate	18%	32%	24%	35%
PD-L1 CPS ≥1	88%	85%	85%	83%
HER2 IHC 3+	82%	79%	83%	78%
Choice of chemotherapy				
CAPOX	86%	88%	87%	86%
FP	14%	12%	13%	14%

Percentages may not total 100% because of rounding. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Waterfall Plots and Confirmed Response at IA1, Efficacy Population

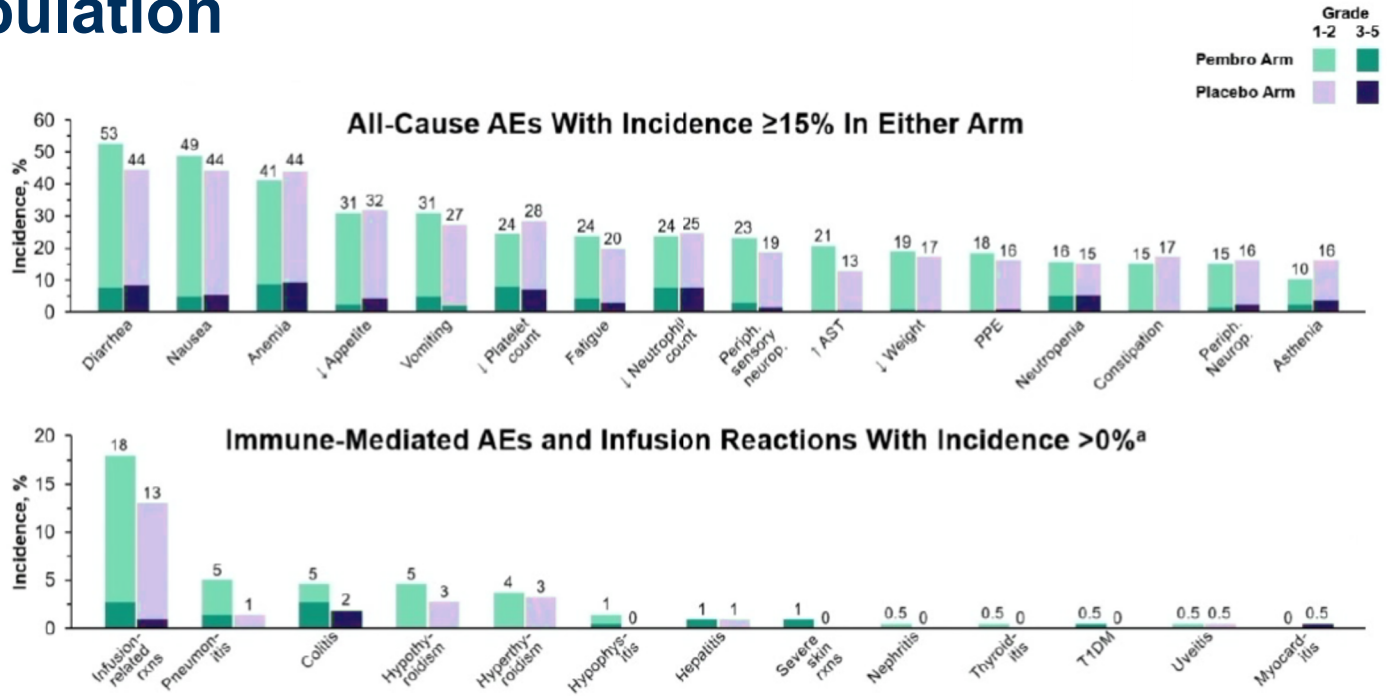


ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[b]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

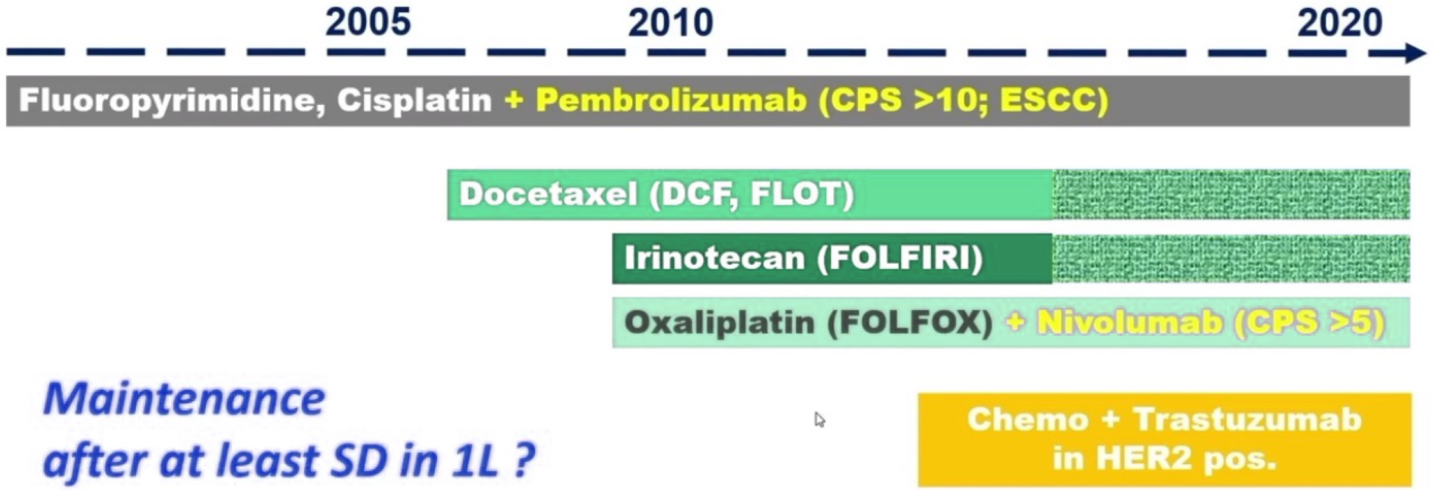
Duration of Response[c]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median[d]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥6-mo duration[d]	70.3%	61.4%
≥9-mo duration[d]	58.4%	51.1%

Most Common Adverse Events at IA1, Safety Population



[a]Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
PPE, palmar-plantar erythrodysesthesia; T1DM, type 1 diabetes mellitus. Participants in both arms received trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Palliative 1L for Adenocarcinoma of Stomach, GE-Junction or Esophagus 2021



FRÉQUENCE MÉDICALE ONCOLOGIE

2021

FRÉQUENCE MÉDICALE ONCOLOGIE

Post ESMO GI 2021

1/ Cholangiocarcinomes

2/ CHC

NalIri/5FU en L2 des cholangiocarcinomes avancés

NIFTY - Design — **Ph II randomisée multicentrique coréenne**

Critères inclusion

- CholangioK M+
- PD après GemCis
- ECOG 0-1
- Mesurable

N=178

R 1 : 1

- **Nal-IRI + 5FU/AF** — N=88
- **5-FU/AF** — N=90

Critère principal:
- **SSP (revue centralisée)**

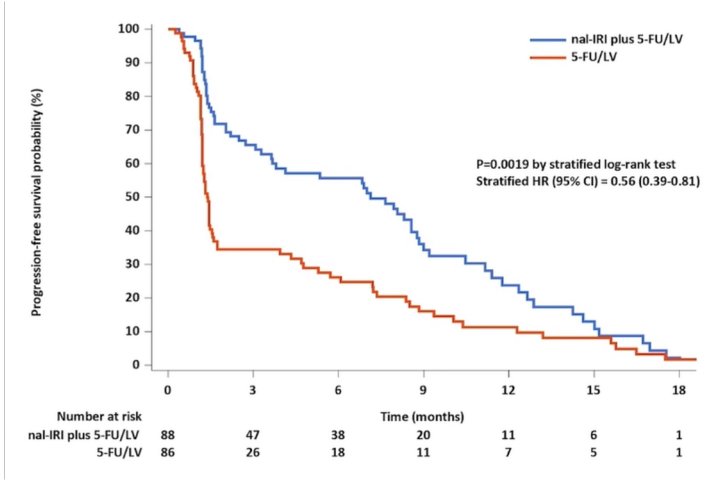
Stratification :
- Localisation (intra- vs extra-hépatique)
- Chirurgie antérieure O/N
- Centre

Nal-IRI: 70 mg/m2 J1
5-FU 2400 mg/m2 J1-J2
Ac folinique : 400 mg/m2 J1

Etude présentée à l'ASCO

NalIri/5FU en L2 des cholangiocarcinomes avancés

NIFTY – SSP (revue centralisée)



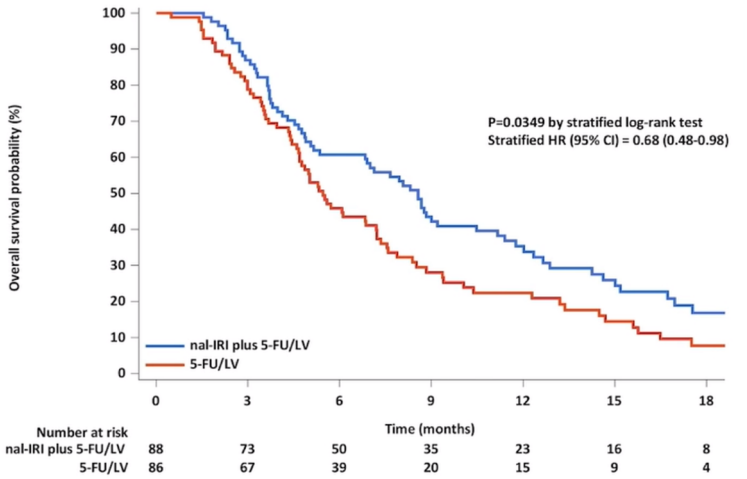
Suivi médian: 11,8 mois

	Nal-IRI + 5-FU/AF	5-FU/AF
SSPm (mois)	**7,1**	**1,4**
	HR 0,56 (IC95%: 0,39-0,81) P=0,0019	
Tx de SSP à 6 mois (%)	**55,7**	**26,2**

Etude présentée à l'ASCO

Nalri/5FU en L2 des cholangiocarcinomes avancés

NIFTY – Survie globale et taux de réponse



	Nal-IRI + 5-FU/AF	5-FU/AF
SGm (mois)	**8,6**	**5,5**
	HR 0,68 (IC95%: 0,48-0,98) p=0,0349	
Tx de SG à 12 mois (%)	**35,4**	**22,4**
Tx de réponse (%) Revue centralisée	**14,8**	**5,8**
	p=0,0684	

Etude présentée à l'ASCO

Conclusion

Étude de phase IIR Coréenne :

- Supériorité en SSP et SG du 5FU+NALIRI vs 5FU seul

- Standard actuel : FOLFOX (phase III ABC-06, FOLFOX > BSC)

Etude présentée à l'ASCO

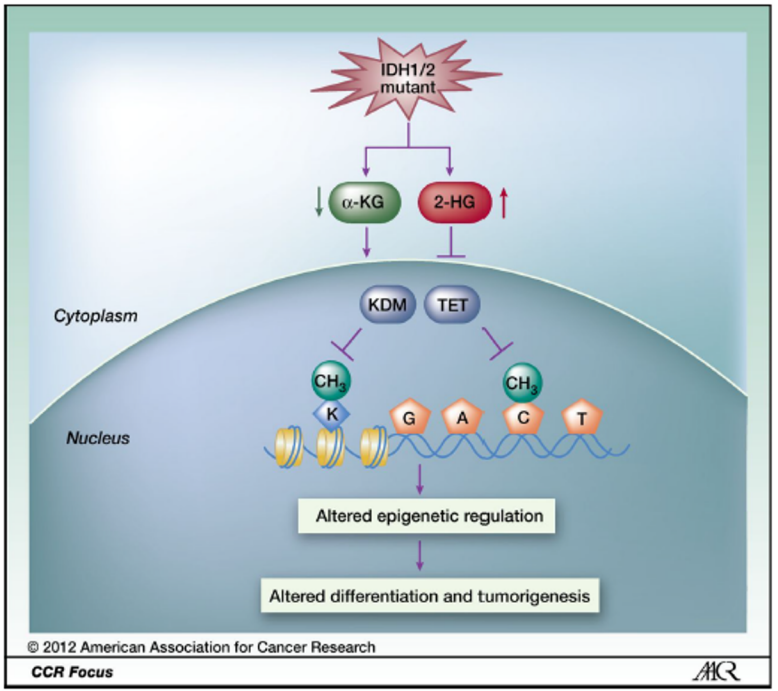
ClarIDHy : résultats finaux

Mutations IDH1 : environ 20% des CCIH

Accumulation de l'oncométabolite 2HG

Ivosidenib (AG-120) :

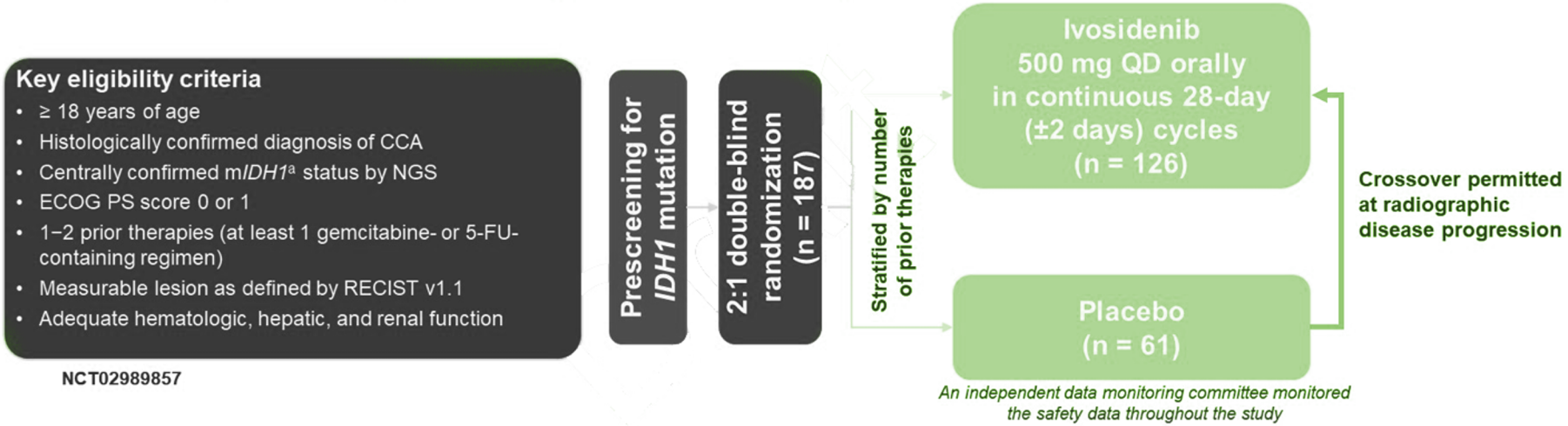
inhibiteur d'IDH1



Hui Yang et al. Clin Cancer Res 2012;18:5562-5571

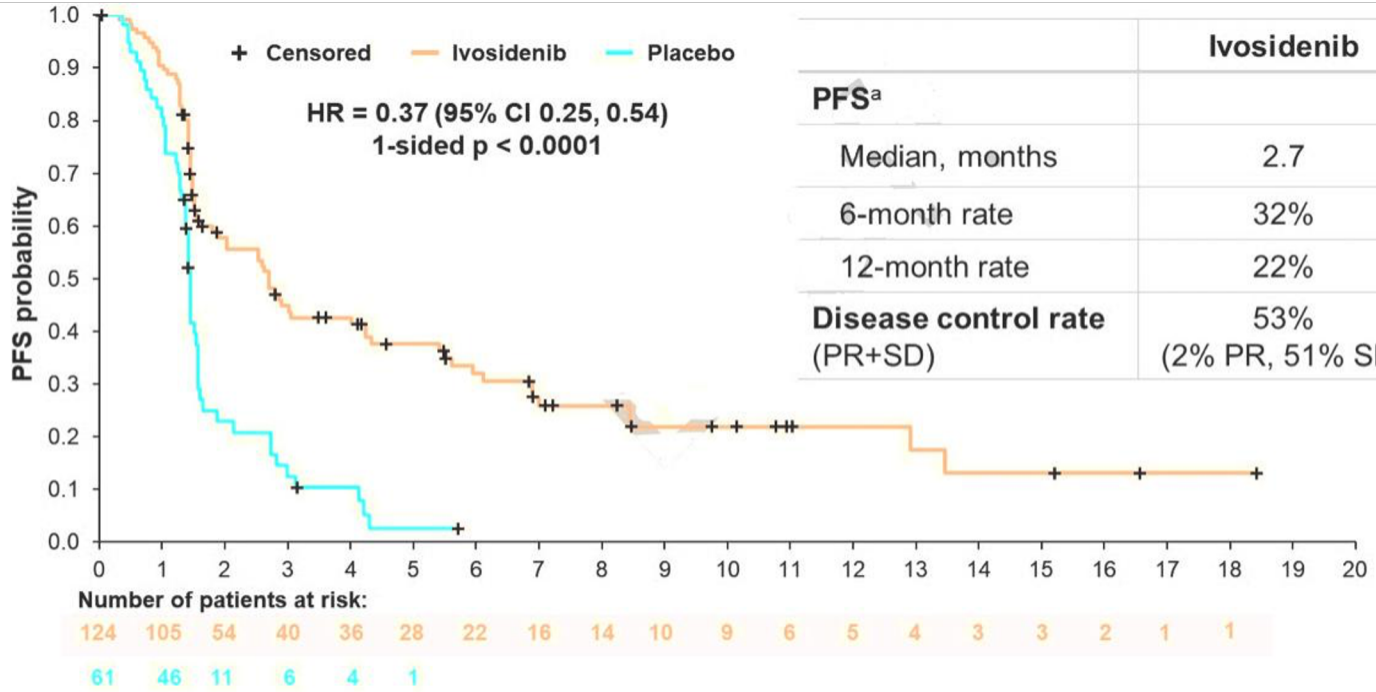
Etude présentée à l'ASCO

ClarIDHy : design



- **Primary endpoint:** progression-free survival (PFS) by blinded independent radiology center (IRC)
- **Key secondary endpoints:** overall survival (OS); objective response rate; PFS by local review; pharmacokinetics/pharmacodynamics; health-related quality of life (HRQOL)[b]; safety and tolerability

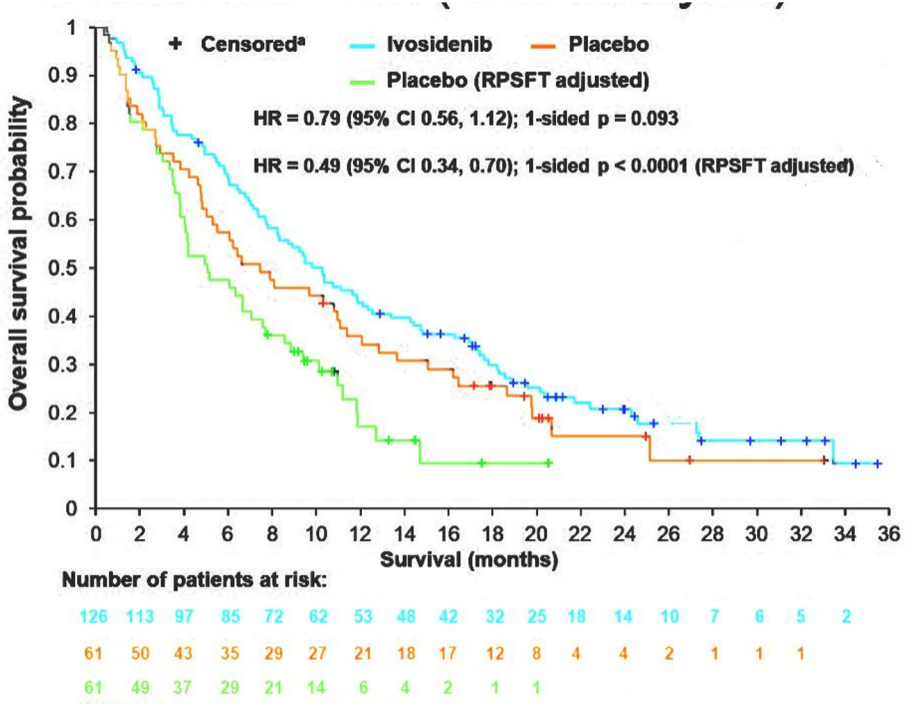
ClarIDHy :
Objectif principal : SSP (relecture centralisée)



	Ivosidenib	Placebo
PFS[a]		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

Etude présentée à l'ASCO

ClarIDHy : Survie globale (analyse finale)



	Ivosidenib n = 126	Placebo n = 61
Number of events (%)	100 (79.4%)	50 (82.0%)
Median OS[b], months	10.3	7.5
6-month rate	69%	57%
12-month rate	43%	36%

- The rank-preserving structural failure time (RPSFT)[1,2] model was implemented as a prespecified analysis to adjust for the effect of crossover from placebo to ivosidenib
- The median OS for placebo after adjustment for crossover was **5.1 months**

Etude présentée à l'ASCO

ClarIDHy

- Ivosidenib : 500mg par jour per os

  ATU nominative en France, 3ème ligne

- Mutation IDH1 (Cholangiocarcinome intrahépatique)

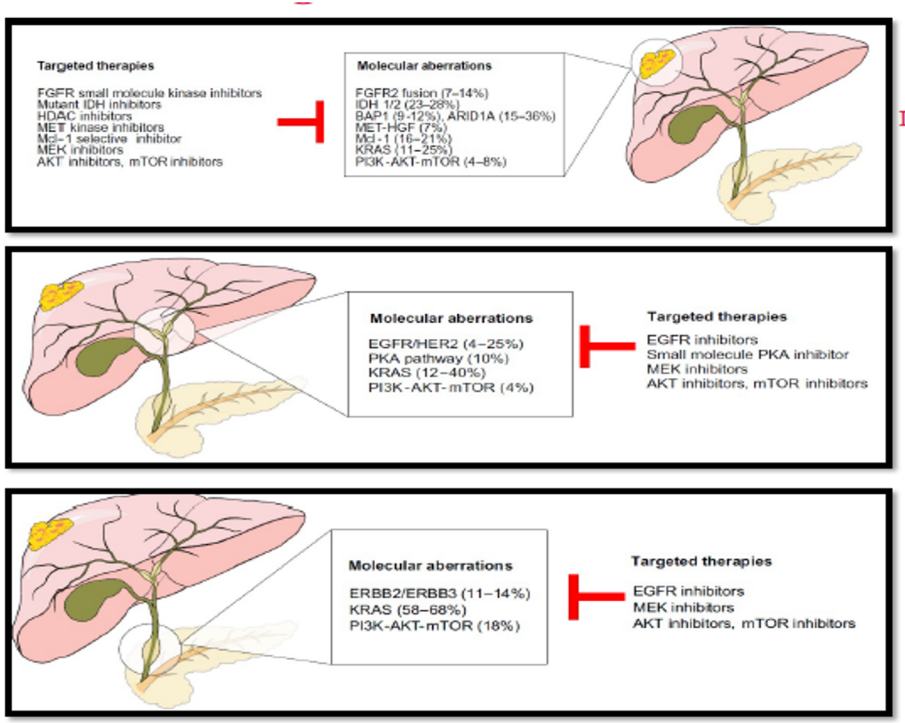
  A rechercher dès que possible au cours de la prise en charge

Etude présentée à l'ASCO

FIGHT-202 : analyse secondaire selon réponse aux traitements antérieurs

SO-4 Progression-free Survival in Patients with cholangiocarcinoma with FGFR2 fusions or rearrangements : A FIGHT 202 post-hos Analysis of Prior Systemic Therapy response

Cholangiocarcinomes et cibles moléculaires



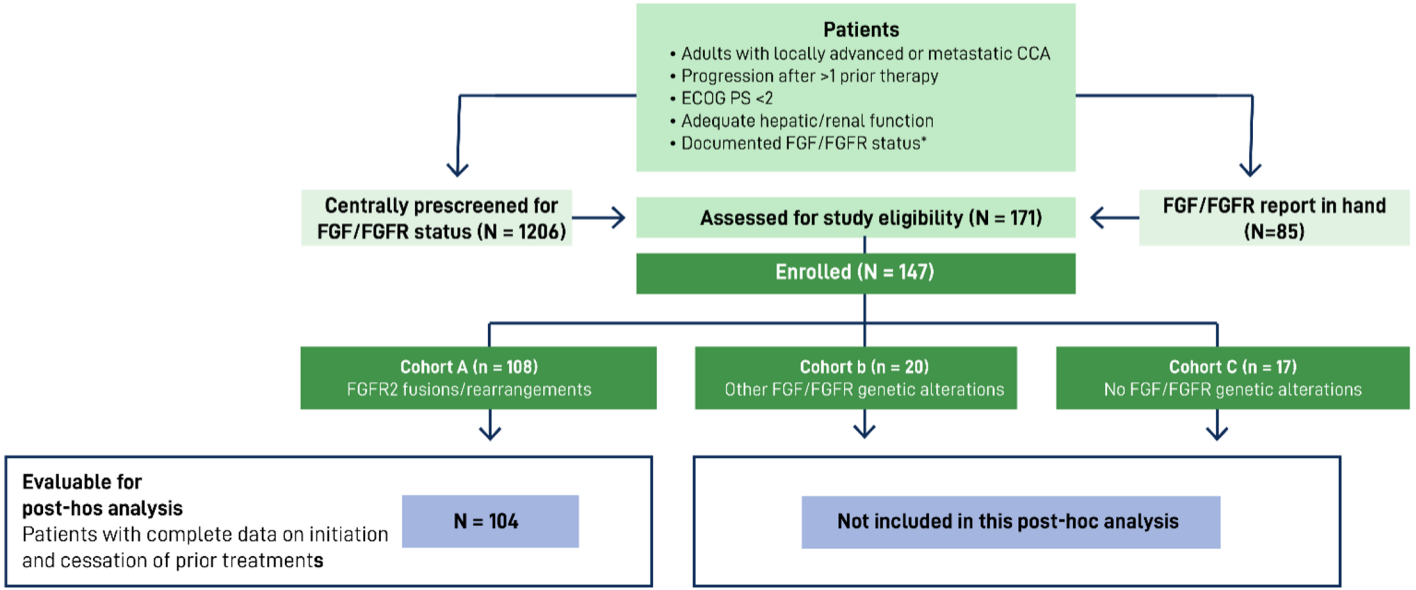
Intrahepatic Cholangiocarcinoma

Perihilar Cholangiocarcinoma

Distal Cholangiocarcinoma + Gallbladder Cancer

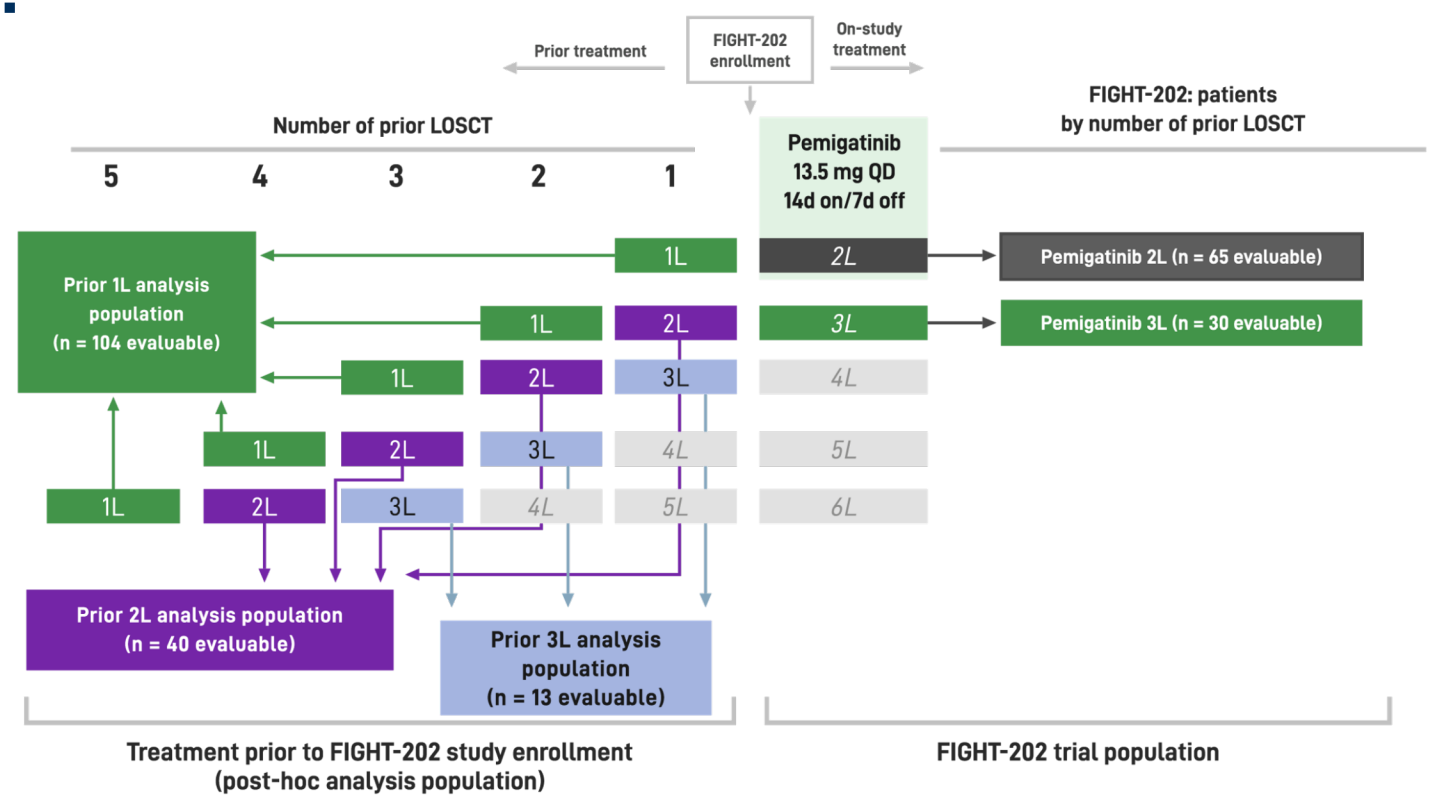
FIGHT-202 : Design

FIGHT-202 is a phase 2 study of pemigatinib in patients with locally advanced or metastatic CCA with or withour FGF/FGFR genomic aterations who progressed on ≥1 prior therapy (NCT02924376)



Résultats :

- Analyse Avril 2020 : 108 patients atteints de CCA avec fusion ou réarrangement FGFR2
- CCIH : 99% des patients, et 61% de femmes

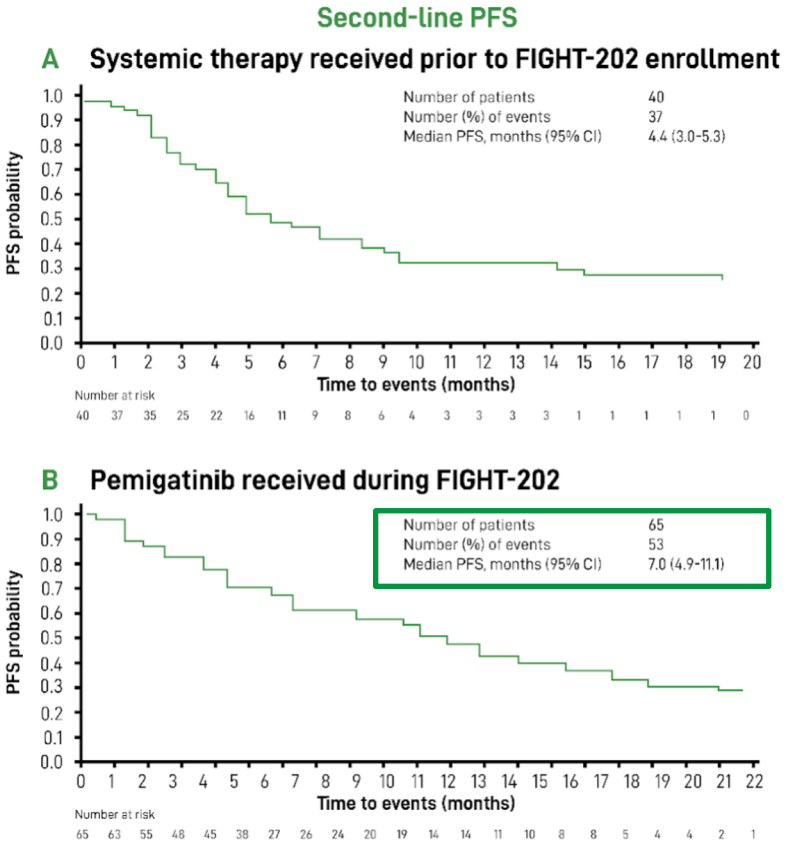


FIGHT-202

- SSP de la chimiothérapie en première ligne :

5.6 mois (n = 104)

(95% confidence interval [CI] 4.0-8.3)

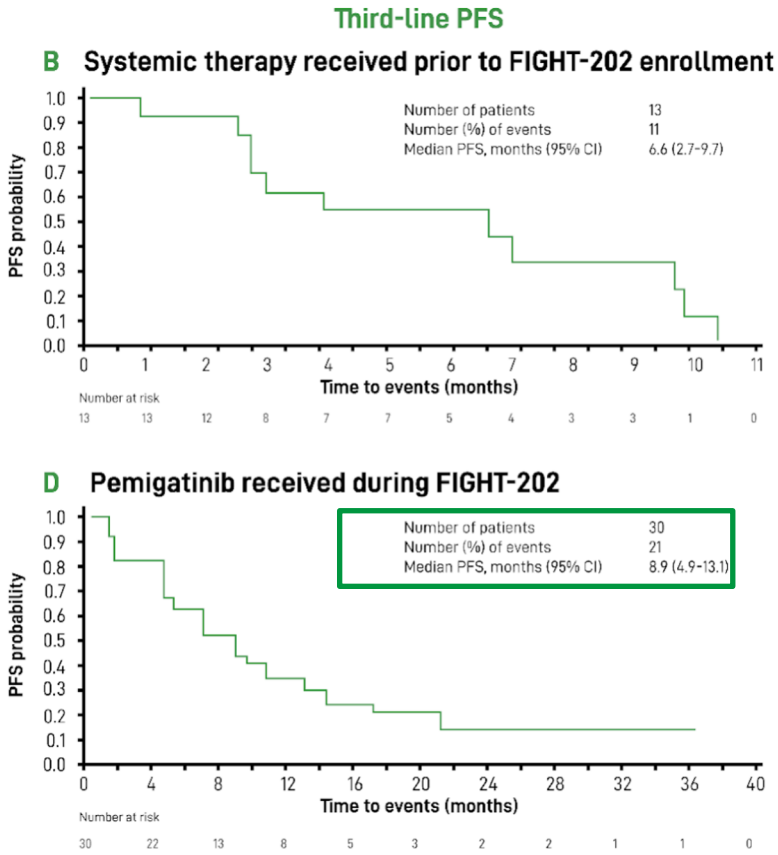


FIGHT-202

- SSP de la chimiothérapie en première ligne :

5.6 mois (n = 104)

(95% confidence interval [CI] 4.0-8.3)



FIGHT-202

- Cholangiocarcinome + altération FGFR2 : 104 patients

- Faible SSP des traitements systémiques en L1 : médiane de 5,6 mois
(8 mois avec GEMCIS dans étude de Valle et al. NEJM 2010)

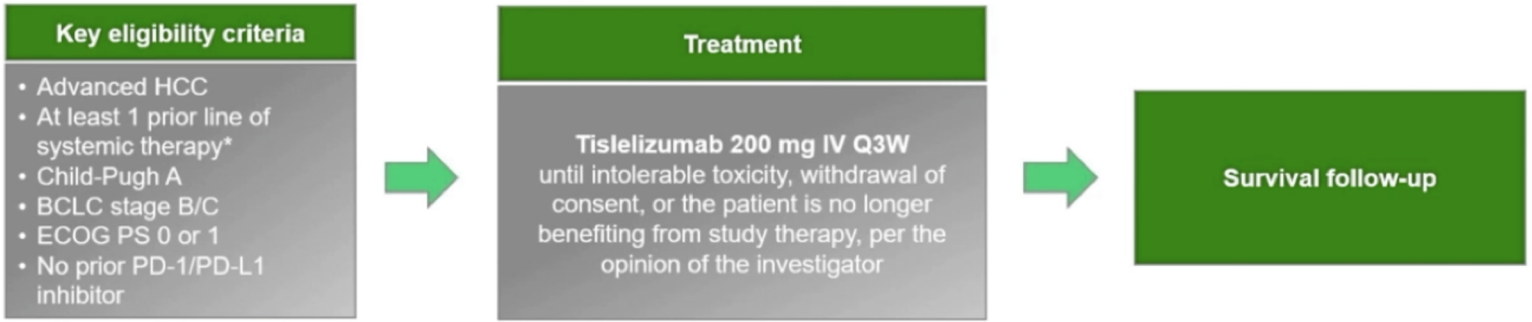
- Pemigatinib : amélioration de la PFS en 2ème et 3ème ligne, par rapport aux traitements systémiques reçus en ligne similaire.

FIGHT-302 en cours de recrutement : Phase III CCK L1 altération FGR2, pemigatinib vs GEMCIS

CHC

Results from a global phase 2 study of tislelizumab, an inverstigational PD-1 antiibody, in patients with previously treated advanced hepatocellular carcinoma

Rationale 208: Tislelizumab en 2ème ligne CHC phase 2 simple bras



Radiological assessments were performed every 6 weeks for the first 18 weeks and then every 9 weeks thereafter

*At least 100 patients were to be enrolled who had 1 line of prior systemic therapy; at least 100 patients were to be enrolled who had ≥2 lines of prior therapy

- Primary endpoint was ORR by IRC per RECIST v1.1
- Secondary endpoints included:
  - DOR, PFS, DCR, and CBR assessed by IRC, and OS
  - ORR, DOR, PFS, DCR and CBR assessed by investigators
  - The safety/tolerability profile of tislelizumab

Rationale 208 : Tislelizumab en 2ème ligne CHC

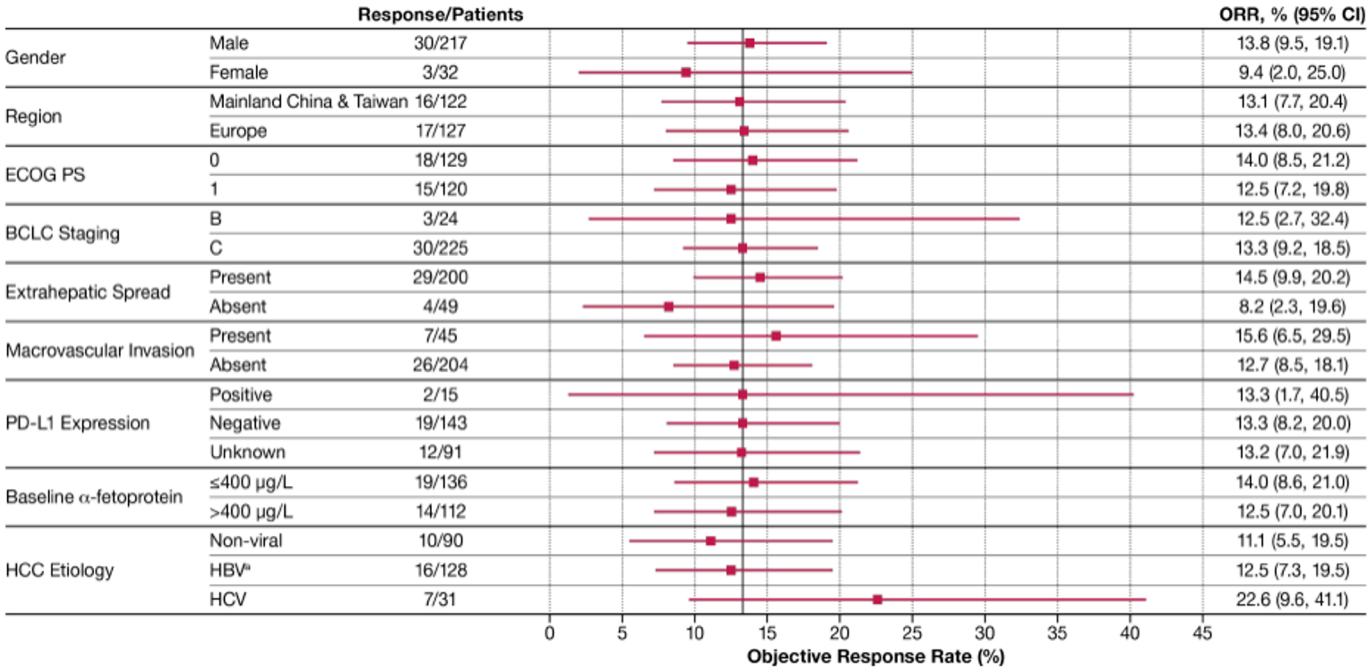
Taux de réponse RECIST 1.1

	Overall (N=249)	1 prior line (n=138)	≥2 prior lines (n=111)
ORR (CR+PR), % (95% CI)	**13.3 (9.3, 18.1)**	**13.8 (8.5, 20.7)**	**12.6 (7.1, 20.3)**
CR, n (%)	3 (1.2)	2 (1.4)	1 (0.9)
PR, n (%)	30 (12.0)	17 (12.3)	13 (11.7)
SD, n (%)	97 (39.0)	52 (37.7)	45 (40.5)
PD, n (%)	107 (43.0)	60 (43.5)	47 (42.3)
Not assessable, n (%)[a]	10 (4.0)	5 (3.6)	5 (4.5)
DCR (CR+PR+SD), % (95% CI)	**53.0 (46.6, 59.3)**	**52.9 (44.2, 61.5)**	**53.2 (43.5, 62.7)**
CBR (CR+PR+SD ≥24 weeks), % (95% CI)	**24.1 (18.9, 29.9)**	**26.1 (19.0, 34.2)**	**21.6 (14.4, 30.4)**
Response duration ≥12 months, % (95% CI)[b]	**79.2 (59.3, 90.2)**	**82.6 (55.2, 94.1)**	**73.0 (35.3, 90.9)**

- Antitumor activity assessed by investigator was similar to IRC

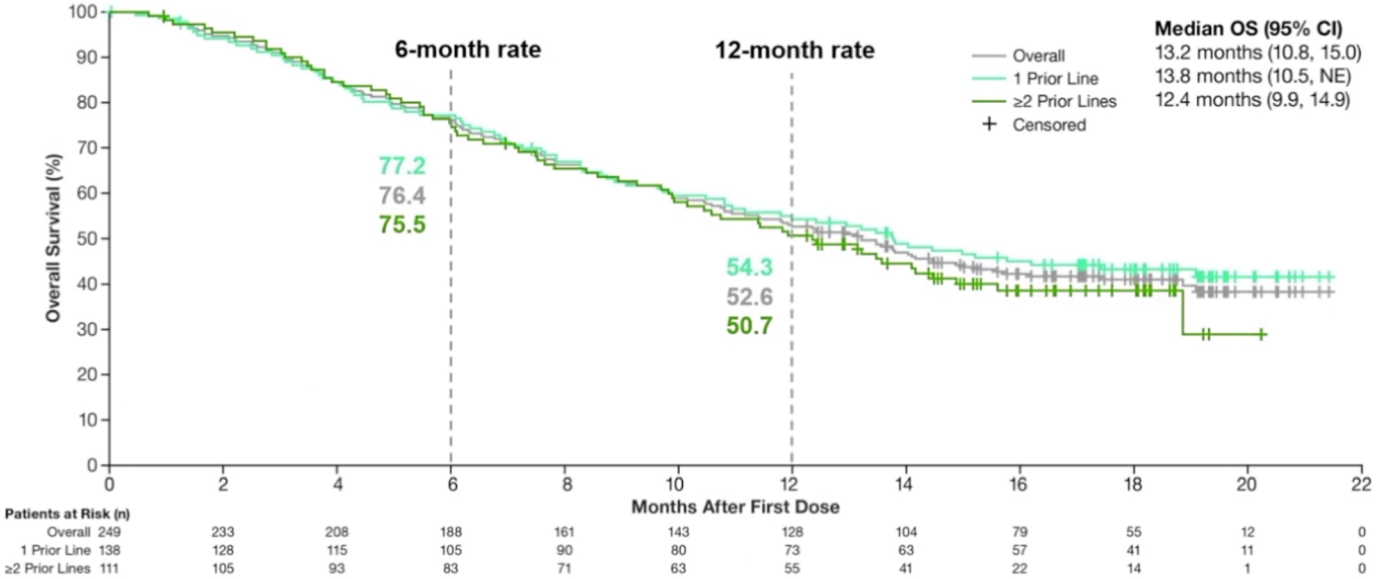
Rationale 208 : Tislelizumab en 2ème ligne CHC

Taux de réponse : analyse de sous-groupes



Rationale 208 : Tislelizumab en 2ème ligne CHC

Survie globale



FRÉQUENCE MÉDICALE ONCOLOGIE

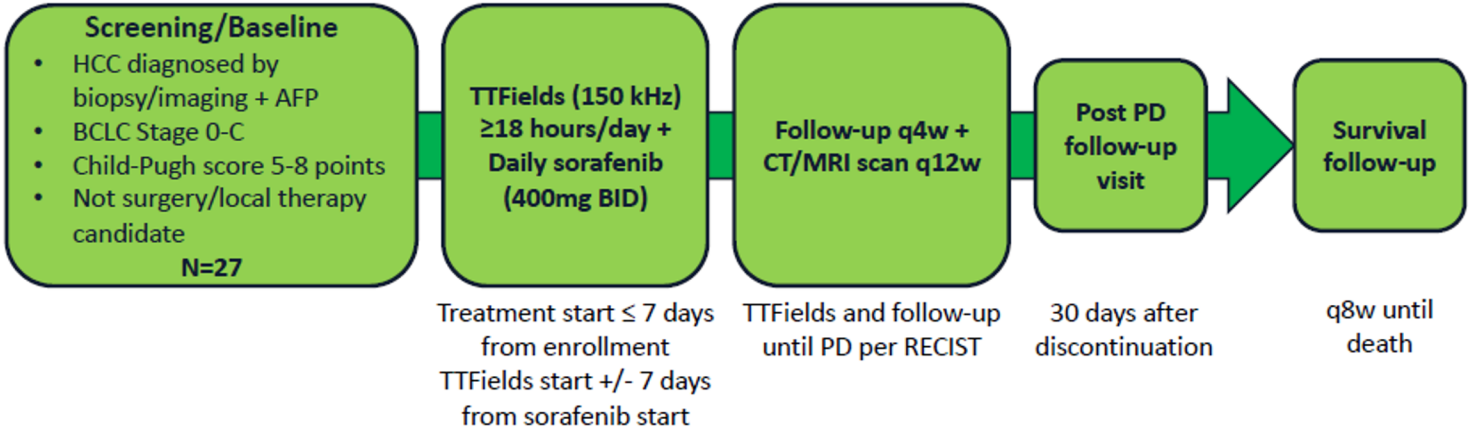
CHC : HEPANOVA

Hepanova: Final Efficacy and Safety Results from a phase 2 Study of Tumor Treating Fields (TTFields, 150 kHz) Concomitant with sorafenib in Advanced Hepatocellular Carcinoma

CHC : HEPANOVA

HEPANOVA Study Design (NCT03606590)

A prospective phase 2, single arm, historical control study testing the efficacy and safety of TTFields concomitant with sorafenib in patients with advanced HCC



A sample size of 25 patients provides 80% (α, 0.05) to detect an ORR of 20% vs 4.5% calculated from historical data[1-4]

Primary Endpoint: Investigator-assessed ORR per RECIST
Main Secondary Endpoints: PFS12; 1 year survival rate; distant metastases-free survival rate at 1 year; safety.

CHC : HEPANOVA

- Caractéristiques patients et traitement

Baseline characteristics	TTFields + Sorafenib (N=27)
Median age, years (Range)	65 (28-85)
Male, No. (%)	26 (96.3)
ECOG performance status, No. (%)	
0	12 (44.4)
1	9 (33.3)
2	6 (22.2)
Child-Pugh score, No. (%)	
5	9 (33.3)
6	4 (14.8)
7	10 (37.0)
8	4 (14.8)
BCLC Stage, No. (%)	
0	1 (3.7)
B	5 (18.5)
C	21 (77.8)
Median Time from Diagnosis to Enrollment, Weeks (Range)	25.6 (1.9-345.9)

Treatment adherence	TTFields (N=27)	Sorafenib (N=27)
No of patients starting treatment (%)	27 (100)	23 (85.2)
Median duration, weeks (Range)	10 (1.3-72.3)	9 (0-72.3)
TTFields mean usage time (% of 24h)	64	NA

CHC : HEPANOVA

Efficacy Results

Outcome	TTFields ≥ 12 weeks + Sorafenib* (N=11)	TTFields + Sorafenib (N=21)
Overall Response Rate, %	18	9.5 (P=0.24)
Level of response, %		
Complete	0	0
Partial	18	9.5
Stable disease	73	66.5
Disease Control Rate, %	91	76

Outcome	TTFields + Sorafenib (N=27)
In-field control rate at 1 year, % (95% CI)	9.5%
Median PFS, months (95% CI)	5.8 (3.0-8.9)
Median time to progression, months (95% CI)	8.9 months (3.1, not reached)
PFS12, % (95% CI)	23 (7-45)
1 year survival rate, % (95% CI)	30 (11-52)
Distant metastases-free survival rate at 1 year, % (95% CI)	26 (8-49)

CHC : HEPANOVA

Association TTFields 150 kHz + Sorafenib :

Étude de phase 2, monobras, 27 patients

- Population de mauvais pronostic (52% Child B7-8, 22% ECOG 2)

Taux de réponses 9,5%

TTFields et immunogénicité tumorale ?

- Association avec Atézolizumab-bevacizumab ?

FRÉQUENCE MÉDICALE ONCOLOGIE

2021

FRÉQUENCE MÉDICALE ONCOLOGIE

Post ESMO GI 2021

1/ Cancers du pancréas
2/ Tumeurs neuro-endocrines

Cancer du pancréas

LBA-1 - Margaret A Tempero
Phase III APACT trial of adjuvant nab-paclitaxel plus gemcitabine vs gemcitabine alone in patients with resected pancreatic cancer: updated 5-year overall survival

LBA-1, Tempero et al, Phase III APACT Trial

- APACT
  - Phase III randomisée : Gem-Nab vs Gem en adjuvant 6 mois
  - ASCO 2019 : étude négative sur son critère principal (survie sans progression, évaluation indépendante)
    - ➔ **DFS 19,4 mois vs 18,8 mois**
    - ➔ **HR, 0.88; (95% CI, 0.729 - 1.063;) stratified log-rank *P* = 0.1824**
  - OS = Critère secondaire : tendance à l'amélioration 40.5 mo (*nab*-P/G) vs 36.2 mo (G)
    (HR, 0.82; 95% CI, 0.680 - 0.996; nominal *P* = 0.045)
  - Effets secondaires liés aux traitements Grade ≥ 3
    - Neutropénie: nab-P + Gem : 49 % vs Gem 43%, Anémie (15% vs 8%) et fatigue (10% vs 3%);
    - 15% vs 0% de neuropathie périphérique

LBA-1, Tempero et al, Phase III APACT Trial

Patients
- > 18 years of age
- Confirmed resected PDAC
- R0/R1
- ECOG PS 0 or 1
- CT without evidence of disease
- CA19-9 < 100 U/Ml
- No prior therapy

Stratification factors
- Resection status (R0 vs R1)
- Lymph node status (positive vs negative)
- Region (North America, Europe, and Australia vs Asia Pacific)

R
1 : 1

n = 432

nab-P 125 mg/m2 qw3/4 +
Gem 1000 mg/m2 qw3/4
x 6 cycles

n = 434

Gem 1000mg/m2 qw3/4
x 6 cycles

Primary endpoint
Independently assessed DFS

Secondary endpoints
- OS
- Safety

Exploration endpoints
- Molecular profiling of tumor tissue
- identification of tumor nucleis acids from blood
- Quality of life

- **Patients were randomized as early as possible after adequate recovery from surgery but nno later than 12 weeks after surgery**
- **Treatment was for 6 cycles until recurrence, death, unacceptable toxicity, consent withdrawal, or patient/physician decisionn**

LBA-1 - Margaret A Tempero – ESMO-GI 2021

LBA-1, Tempero et al, Phase III APACT Trial

Baseline demographics and clinical characteristics

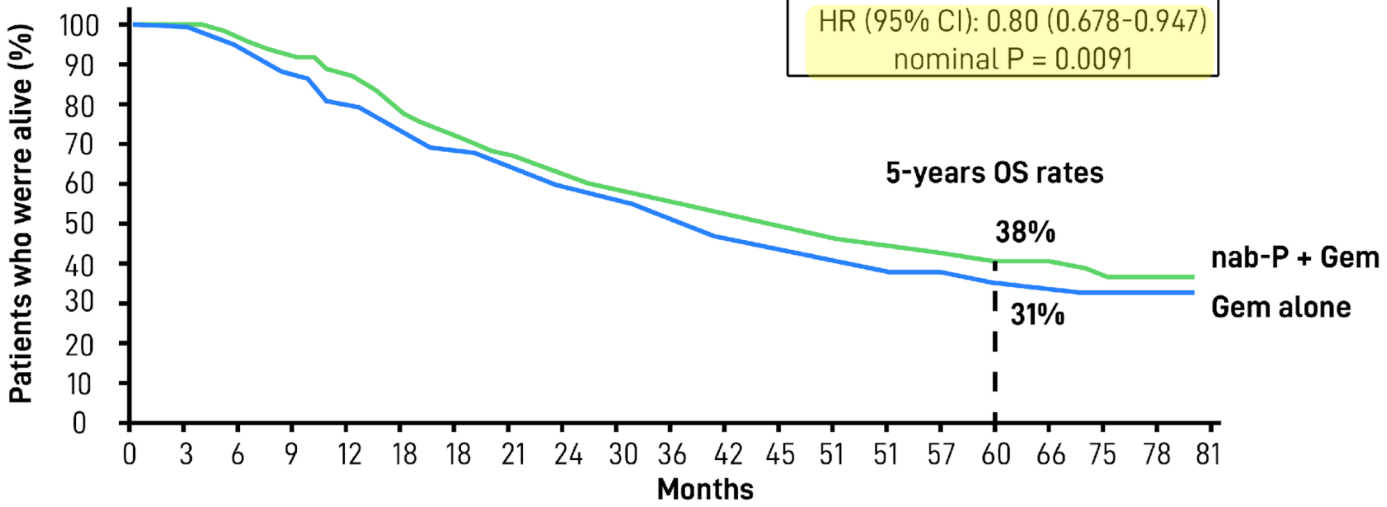
	nab-P + Gem nn = 432	Gem n = 434
Age, median (range), years	64.0 (34-83)	64.0 (34-83)
Male, n (%)	228 (53)	253 (58)
ECOG PS, n (%)		
0	252 (58)	268 (62)
1	180 (42)	166 (38)
Resection status, n (%)		
R0 (tomor-free margin)	327 (76)	334 (77)
R1 (microscopically positive margin)	105 (24)	105 (24)
Nodal status, n (%)		
Negative	121 (28)	121 (28)
Positive	311 (72)	311 (72)
Baseline CA19-9		
n	423	429
Median (range), U/mL	14.31 (1.00-255.28)	12.90 (1.00-275.87)
Tumor stage, n (%)		
T1	16 (4)	13 (3)
T2	38 (9)	38 (9)
T3	377 (87)	384 (88)
T4	1 (<1)	0
Distance from tumor closest margin, n (%)		
<1 mm	114 (26)	112 (26)
>1 mm	287 (66)	292 (67)
Missing	31 (7)	30 (7)

LBA-1 - Margaret A Tempero – ESMO-GI 2021

Actualisation survie globale à 5 ans

	Events	Medan, mo
nab-P + Gem	268/432	41.8
Gem alone	287/434	37.7

HR (95% CI): 0.80 (0.678-0.947)
nominal P = 0.0091

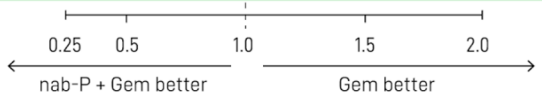


LBA-1 - Margaret A Tempero – ESMO-GI 2021

Actualisation survie globale à 5 ans

Prespecified subgroup analysis: OS (cont)

Subgroup	nab-P + GEM (No. of events/patients)	GEM (No. of events/patients)	HR for death (95% CI)
All patients			
Pancreatic cancer primary location			
Head	229/354	238/347	0.84 (0.705-0.983)
Other	39/78	49/87	0.88 (0.658-1.040)
Tumor grade			
Well differentiated	25/49	31/55	0.88 (0.654-1.065)
Moderately differentiated	164/264	172/241	0.74 (0.653-1.078)
Poorly differentiated	70/101	72/115	1.04 (0.667-1.041)
Resectionn status			
R0	190/327	210/334	0.85 (0.559-0.998)
R1	78/105	77/100	0.73 (0.721-1.164)
Nodal status			
LN positive	215/311	231/312	0.77 (0.405-1.683)
LN negative	53/121	56/122	0.97 (0.405-1.183)
Level of CA19-9 at baseline			
WNL	208/351	226/345	0.82 (0.645-0.993)
ULN < 100 U/mL	51/70	59/81	0.82 (0.674-1.143Z
>100 U/mL	2/2	2/3	



LBA-1 - Margaret A Tempero – ESMO-GI 2021

Actualisation survie globale à 5 ans

	5-y-OS Con, %	5-y-OS Exp, %	R0%	T4%	N1%
APACT	31	38	77/76	0/1	72/72
PRODIGE	27	48	54.5/59/9	2/3.2	63/73
JASPAC	24	44.1	86/88	0/1	62/64
ESPAC4	16	28.8	40/39	n.r.	82/79
CONKO-001	10	20.7	85/81	3/4	71/70

LBA-1 - Margaret A Tempero – ESMO-GI 2021

Actualisation survie globale à 5 ans

Etude négative sur son critère principal: indep. PFS

Amélioration significative de l'OS (critère secondaire)

mFOLFIRINOX reste le standard, surtout si facteurs péjoratifs (T4,R1, N+)

Intérêt Gem-NabPaclitaxel dans la population non éligible au folfirinox ? (>75ans? PS2?) ➔ donnée prospective?

Perspective avec les futures lignes en néoadjuvant

Cancer du pancréas

SO-2: Syed Ali Amir Sherazi
Pancreatic Cancer in HIV versus Non-HIV population – Analysis of Demographics, Outcomes and Healthcare Utilization from a national sample

Particularité population VIH+ avec un ADK du pancréas

- Efficacité des nouveaux anti-viraux
- Augmentation du risque de PDAC chez patients VIH+?
  - Données contradictoire (x 2,5 aux USA vers aucun sur risque)
  - Base de donnée de consommation de soin US, 2016-2018

	HIV-PC	Non-HIV-PC	P-value
Total admissions	775	317.4	n/a
Mean age (years)	59.9	68.1	<0.001
>65 years old	29.7 %	63.3	<0.001
Men	71 %	53%	<0.0001
Black	52 %	14%	<0.0001
White	34 %	71 %	<0.0001
Teaching hospitals	84 %	76 %	0.047
Medicaid insurance	30 %	8.6 %	<0.001
Comorbidities	CKD	HTN	<0.05
	Dialysis	Dyslipidemia	<0.05

→

	HIV-PC	Non-HIV-PC	P-value
Mean LOS	7.5 days	6.1 days	0.001
Adjusted LOS (patient and hospital demographics)			**Not Significant**
Mean THC	$80.000	$66.000	0.02
Adjusted THC (patient and hospital demographics)			**Not Significant**
Absolute mortality	9.0%	7.6%	**Not Significant**
Adjusted Odds Ratio (aOR) mortality = 0.43 (95%CI 0.24-0.76) p=0.004			

SO-2: Syed Ali Amir Sherazi – ESMO-GI 2021

VIH + et PDAC : Population à prendre en compte :

- Patients plus jeune
- Plus fragiles/comorbides ? (Italian Cohorte, *Zanet et al, 2012* -> PS>2 + fréquent)
- Pas plus de consommation de soins mais imputabilité direct du VIH difficile à évaluer
- Plus de risque de mortalité toute cause → toxicité ou échec des ttt? Autre causes??
- Particularité moléculaires tumorales?

FRÉQUENCE MÉDICALE ONCOLOGIE

Cancer du pancréas

SO-3: Julien Taïeb
Treatment sequences and prognostic factors in metastatic pancreatic ductal adenocarcinoma: univariate and multivariate analyses of a real-world study in Europe

Séquences thérapeutiques PDAC métastatique en Europe

- Panorama du traitement PDAC en Europe
- - 5 pays, 6000 patients inclus
  - Données de traitement L1 / L2 et de suivie 5 ans

TREATMENT SEQUENCES AND PROGNOSTIC FACTORS IN METASTATIC PANCREATIC DUCTAL ADENOCARCINOMA: UNIVARATE AND MULTIVARIATE ANALYSES OF A REAL-WORL STUDY IN EUROPE

- What is the therapeutic landscape in metastatic PDAC in Europe?
- 5 countries, records from date of diagnosis to 5 years or death
- 60000 online reports, 915 patients with data on 1l and 2l treatment for COX regresssion of prognostic factors

SO-3: Julien Taïeb – ESMO-GI 2021

Première et deuxième ligne de traitement

Baseline characteristics per 1L treatment (n=3432)*

	(m)FOLFIRINOX	5-FU + ox	Gem + nab-pac	Gem + other	Gem mono
ECOG PS 0/1, %	86.1	75	73.2	60.7	27.7
ECOG PS ≥2, %	13.9	23.9	26.8	39.3	72.3
Male, %	65.2	61.7	59.0	56.4	54.2
Female, %	34.8	38.3	41.0	43.6	45.8
Age at mPAC, y	60.7	62.6	65.4	65.2	73.3
CA19-9 <400 U/ml, %	44.2	36.7	38.0	67.2	33.6
CA19-9 ≥400 U/ml, %	55.8	63.3	62.0	32.8	66.4

* Patients treated with (m)FOLFIRINOX had more favourable baseline characteristics vs. other 1L treatment regimens.

Six most common treatments (1L)

- (m)FOLFIRINOX : 974 (28.4%)
- Gem + nab-pac: 961 (28%)
- Gem mono: 790 (23%)
- Other gem-based: 369 (10.8%)
- FPyr + oxaliplatin: 188 (5.5%)
- Other: 150 (4.3%)

Six most common treatment sequences (1L→2L)

- Gem + nab-pac → FPyr combos: 286 (24%)
- (m)FOLFIRINOX → gem combos: 263 (22%)
- (m)FOLFIRINOX → gem mono: 228 (19%)
- Gem + nab-pac → FPyr mono: 65 (5%)
- Gem mono → FPyr mono: 41 (3%)
- Gem mono → FPyr combos: 32 (3%)

ECOG PS, Eastern Cooperative Oncology Group Performance Status.
(m)FOLFIRINOX, modified folinic acid, fluorouracil, irinotecan and oxaliplatin. FPyr, fluoropyrimidines. Gem, gemcitabine. Mono, monotherapy. Nab-pac, nab-paclitaxel.

SO-3: Julien Taïeb – ESMO-GI 2021

Facteurs pronostics et séquence de traitement L1 ➔ L2 influençant la survie (n=915)

Prognostic factors for survival

- No liver metastases HR=0.397 (p<0.0001)
- ECOG PS 0/1 HR=0.448 (p<0.0001)
- CA19-9 <400 U/ml HR=0.747 (p=0.0004)
- No lung metastases HR=0.789 (p=0.0049)
- Male HR=0.828 (p=0.0228)

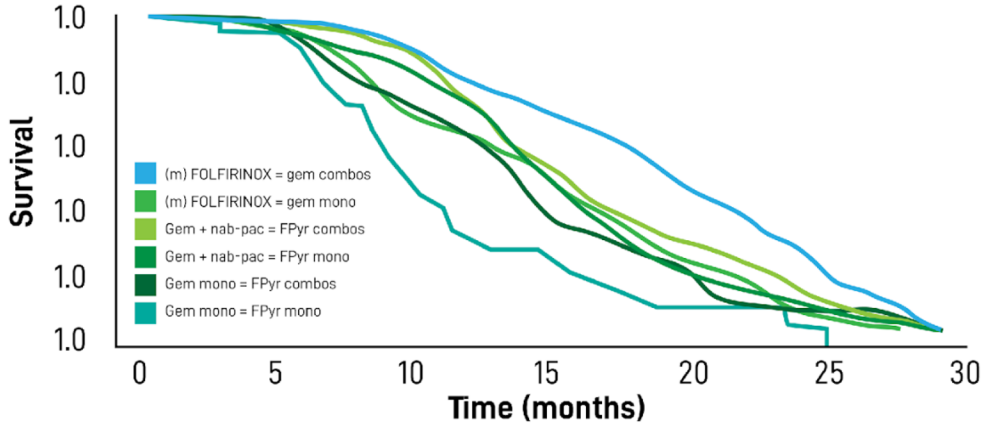
Treatments prognostic for survival (vs. gem mono→FPyr mono)*

- (m)FOLFIRINOX→GEM combos HR=0.424 (0.293,0.615)
- GEM + nab-pac→FPyr combos HR=0.601 (0.418,0.865)
- GEM + nab-pac→FPyr mono HR=0.645 (0.413,1.007)
- (m)FOLFIRINOX→gem mono HR=0.665 (0.461,0.958)
- Gem mono→FPyr combos HR=0.787 (0.465,1.332)

* p<0.0001. Combos, combinations. ECOG PS, ECOG PS, Eastern Cooperative Oncology Group Performance Status.
(m)FOLFIRINOX, modified folinic acid, fluorouracil, irinotecan and oxaliplatin. FPyr, fluoropyrimidine. Gem, gemcitabine. Mono, monotherapy. Nab-pac, nab-paclitaxel.

SO-3: Julien Taïeb – ESMO-GI 2021

Longest mOS with (m)FOLFIRINOX ➔ gem combinations (from start of 1L treatment)



Treatment sequence (1L = 2L)	PS 0/1	PS >2
(m) FOLFIRINOX = gem combos	20.0	12.6
(m) FOLFIRINOX = gem mono	14.8	15.0
Gem + nab-pac = FPyr combos	15.5	12.7
Gem + nab-pac = FPyr mono	15.6	8.3
Gem mono = FPyr combos	15.9	12.8
Gem mono = FPyr mono	10.2	8.8

SO-3: Julien Taïeb – ESMO-GI 2021

Survie la plus favorable sous Folfirinox en L1 ➔ Gem combo en L2

➔ mOS ECOG 0-1 = **20 mois !!** (Prodige 11, 98% ECOG 0-1, : mOS ➔ 11.1 mois)

Facteurs confondants à prendre en compte (patients avec meilleurs ECOG et jeune)

Problématique de remboursement du Gem-NabPaclitaxel entre pays U.E

FRÉQUENCE MÉDICALE ONCOLOGIE

Cancer du pancréas

Chirugie mini invasive -Baki Topal

Surgery for Pancreatic Cancer and Bile Duct Cancer: Are Laparoscopic and Robotic Surgeries the Future?

Chirurgie mini-invasive pour PDAC

22013 Pancreaticoduodenectomy ofr Pancreatic Cancer

TABLE 3. Short term outcomes followinig open versus Minimally invasive Pancreaticoduodenectomy

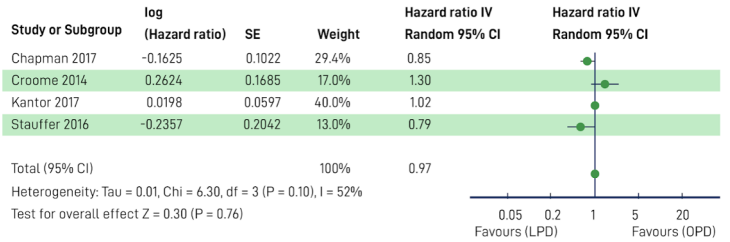
Outcome	n (%)	OR
90 day mortality		
Open	1004 (6%)	Ref
Minimally invasive	144 (5%)	0.92
30 day mortality		
Open	504 (3%)	Ref
Minimally invasive	77 (3%)	1.01
Hospital length of stay		
Open	7697 (43%)	Ref
Minimally invasive	1280 (35%)	0.75
Unplanned 30-day readmission		
Open	1463 (8%)	Red
Minimally invasive	307 (8%)	1.01

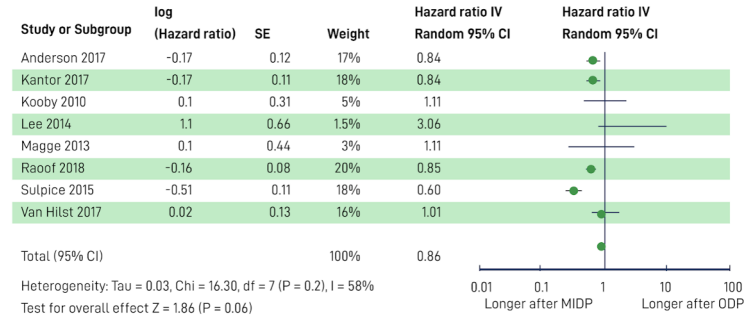
TABLE 4. Oncologic outcomes followinig open versus Minimally invasive Pancreaticoduodenectomy

Outcome	n (%)	OR
Positive margins		
Open	3594 (20%)	Red
Minimally invasive	655 (15%)	0.93
Lymph nodes harvested (>16)		
Open	8220 (45%)	Ref
Minimally invasive	1800 (48%)	0.95
Adjuvant chemotherapy		
Open	8621 (56%)	Ref
Minimally invasive	1732 (57%)	0.98

Baki Topal, ESMO-GI 2021

Survival after MIPS for PDAC





Chirurgie mini-invasive pour PDAC

Revue systématique sur la tolérance et l'efficacité chirurgie laparoscopique vs chirurgie « open » dans la chirurgie pancréas + voie biliaire

- Nombreuses données de centre à haut volume pour la chir. Laparotomie
- Peu de données pour la chirurgie mini-invasive et issues de centres experts

➔ Avantage Laparoscopie

- Diminution temps hospitalisé
- Morbi-mortalité identique
- Survie et efficacité chirurgicale identique
- Etudes comparatives attendues

FRÉQUENCE MÉDICALE ONCOLOGIE

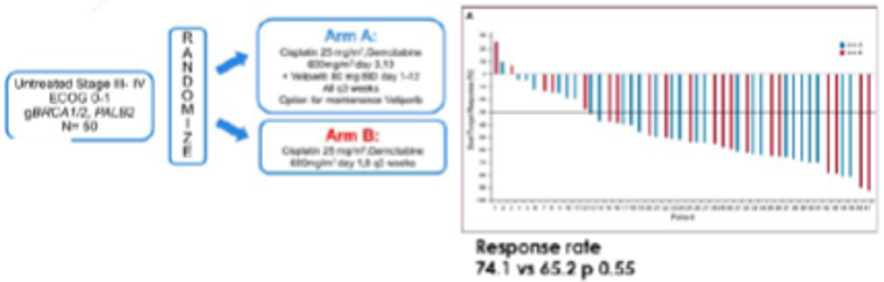
Cancer du pancréas

Conclusions/Perspective Pancreas ASCO – ESMO-GI 2021

Rechercher les anomalies de réparation de l'ADN (BRCA, PALB2, ATM…) Séquence sels de platine et entretient par Anti-PARP

Patients characteristics		Olarparib (N=92)	Placebo (N=62)
Age	Median, years (range)	57.0(32-84)	57.0 (36-75)
Sex, n(%)	Male	53 (57)	31 (50)
ECOG performance status, n(%)	0	65 (70)	38 (61)
	1	25 (27)	23 (37)
BRCA mutation status, n (%)	BRCA 1	29 (32)	16 (25)
	BRCA 2	62 (67)	46 (74)
	Both	1 (1)	0
Time from diagnosis to randomization	Median, months (range)	6.9 (3.6-38)	7.0 (4.1-30)
Duration of first-line chemotherapy	Median, months (range)	5.0 (2.5-35)	5.1(3.4-20.4)
	16 weeks to 5 months, n (%)	61 (66)	40 (64)
	>6 months, n (%)	30 (32)	21 (33.9)
First-line platinum-based chemotherapy n(%)	FOLFIRINOX variants	29 (85.9)	50 (80.6)
	Gemcitabine/cisplatin	2 (2)	3 (4.8)
	Other	10 (10.9)	8 (52.9)
Best response on first-line	Complete of partial response	46 (50)	30 (48)
chemotherapy , n (%)	Stable disease	45 (48.9)	31 (50)
Disease status following	Measurable	78 (84.8)	52 (83)
first-line chemotherapy, n (%)	Non-measurable or no evidence of desease	13 (14.1)	6 (9.7)

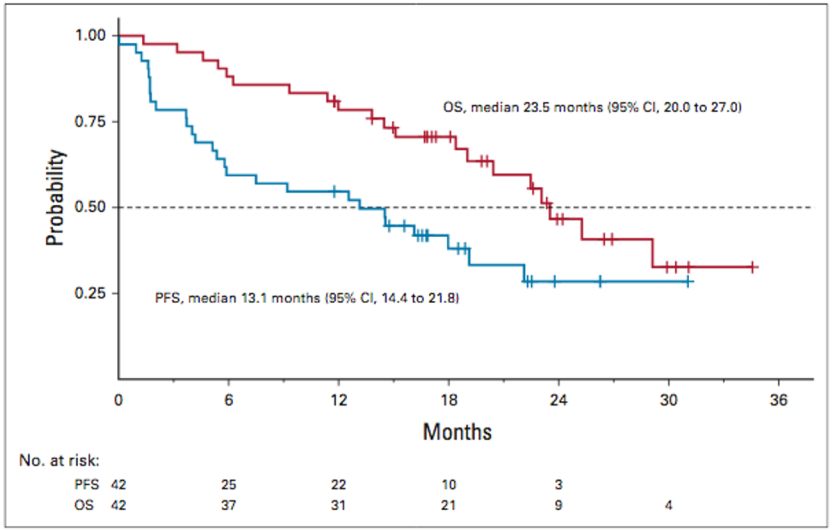
Golan et al, NEJM 2019

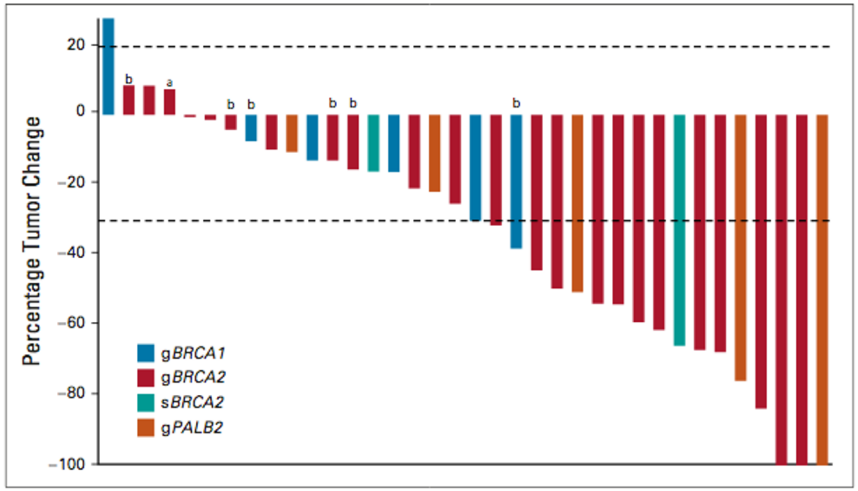


O'Reilly et al, J Clin Oncol 2020

Gemcitabine and cisplatin an active combination for the gBRCA1/2 and PALB2 PDAC patients

Séquence possiblement efficace si mutation somatique





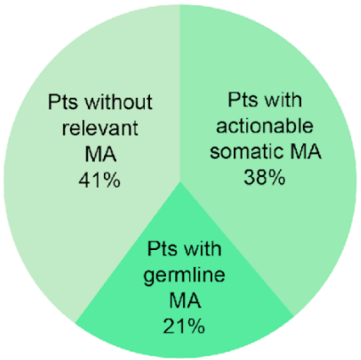
Reiss et al, J Clin Oncol 2021

- N 46 germline or somatic mut BRCA1/2 or PALB2, received at least 16 w of platinum-based chemotherapy with no evidence of resistance.
- PFS: 13.1 m, OS 21.5 m and ORR 41.7% (3 CR), DoR 17.3 m.
- Responses were in gBRCA2, gPALB2 and sBRCA2.

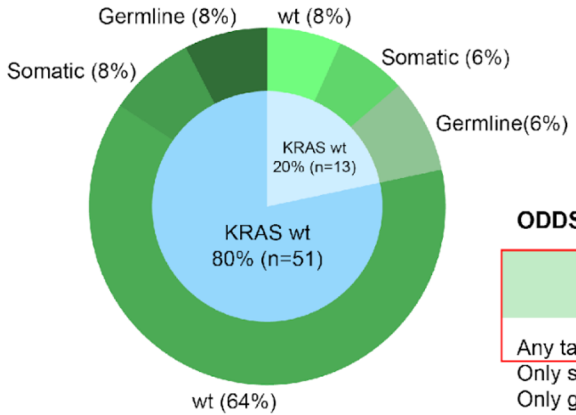
Stratégie de traitement guidé par le NGS

VHIO: KRAS Wild-Type (N=29)

Proportion of pts with targetable MA



VHIO PDAC in patients younger than 50 years:
Clinical outcomes and actionable genomic/genetic alterations



ODDS ratio of targetable alteration in KRAS wt of mutated PC (Fisher test)

	KRAS wt N=13	KRAS ALT N=51	Odds ratio	95% CI	p value
Any targetable atleration	8 (61%)	10 (20%)	5.32	(1.47-30)	0.005
Only somatic alterations	4 (30%)	5 (10%)	3.97	(0.65-22)	0.07
Only germline alterations	4 (30%)	5 (10%)	3.97	(0.65-22)	0.07

Stratégie de traitement guidé par le NGS

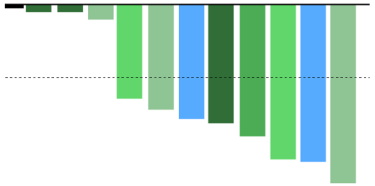
VHIO: KRAS Wild-Type (N= 29)[1]

Molecular alteration	%	n
ATM	9,5%	2
BRAF	4,8%	1
BRCA1	9,5%	2
BRCA2	19,0%	4
CCDC6/RET *	4,8%	1
CDKN2A del	4,8%	1
ENOX2/BRAF*	4,8%	1
ERBB3	4,8%	1
NOTCH1	4,8%	1
NOTCH2/NRG1*	4,8%	1
PALB2	4,8%	1
PIK3CA	4,8%	1
PMS2	4,8%	1
RNF43	9,5%	2
STK11	4,8%	1
Total	100%	21

Germline event
Somatic alteration
DNA damage repair related

Most MA are mutations unless otherwise indicated
* Fusion

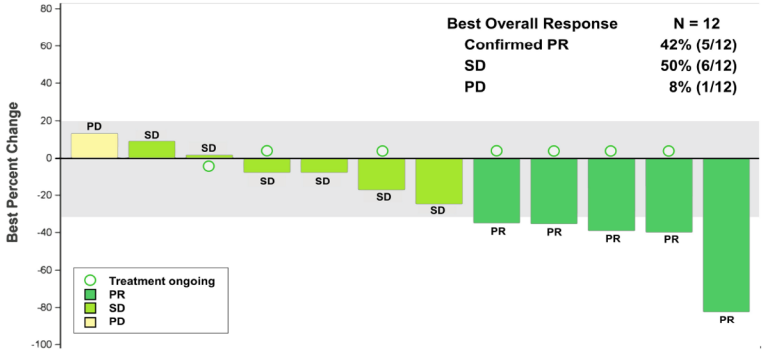
Efficacy of BLU-667 (Pralsetinib) in RET Fusion + tumours



Best response (response evaluable), %	RET fusion-positive tumor (n-12)
DRR (95% CI)	50 (21-79)
PR	50
SD	42
PD	8
DCR (95% CI)	92 (62-100)

Efficacy in NRG1+ PDAC

Best % Change in Target Lesions from Baseline

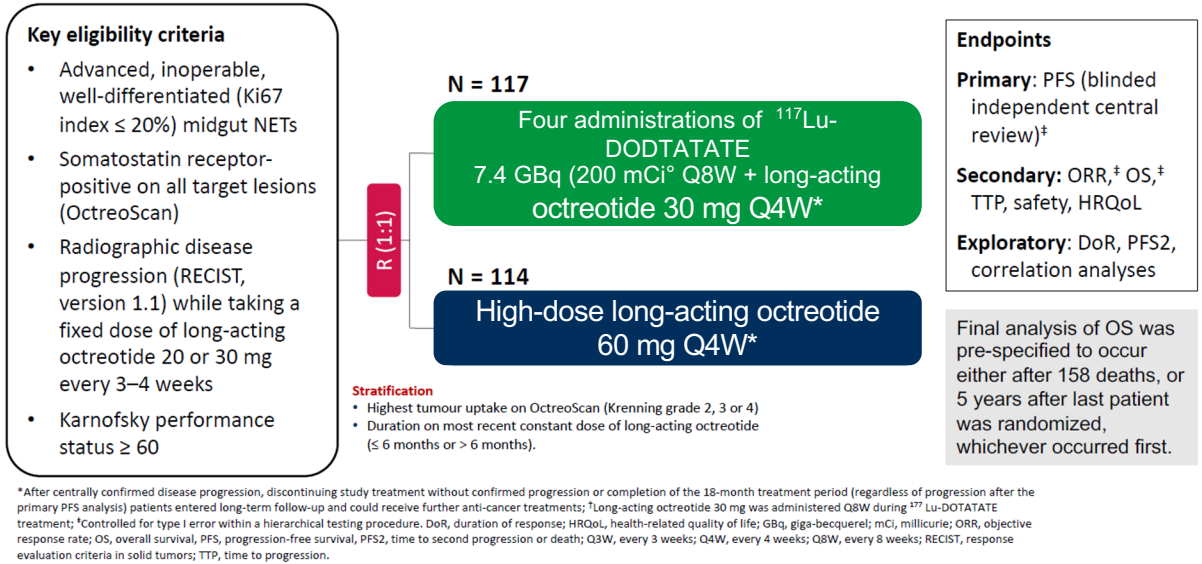


FRÉQUENCE MÉDICALE ONCOLOGIE

Tumeurs Neuro-Endocrine

O-2: Jonathan R. Strosberg
Overall survival and long-term safety data from the NETTER-1 trial: 177-Lu-Dotatate vs. high-dose octreotide in patients with progressive midgut NETs

NETTER-1: Phase III internationale, randomisées, contrôlée en ouvert



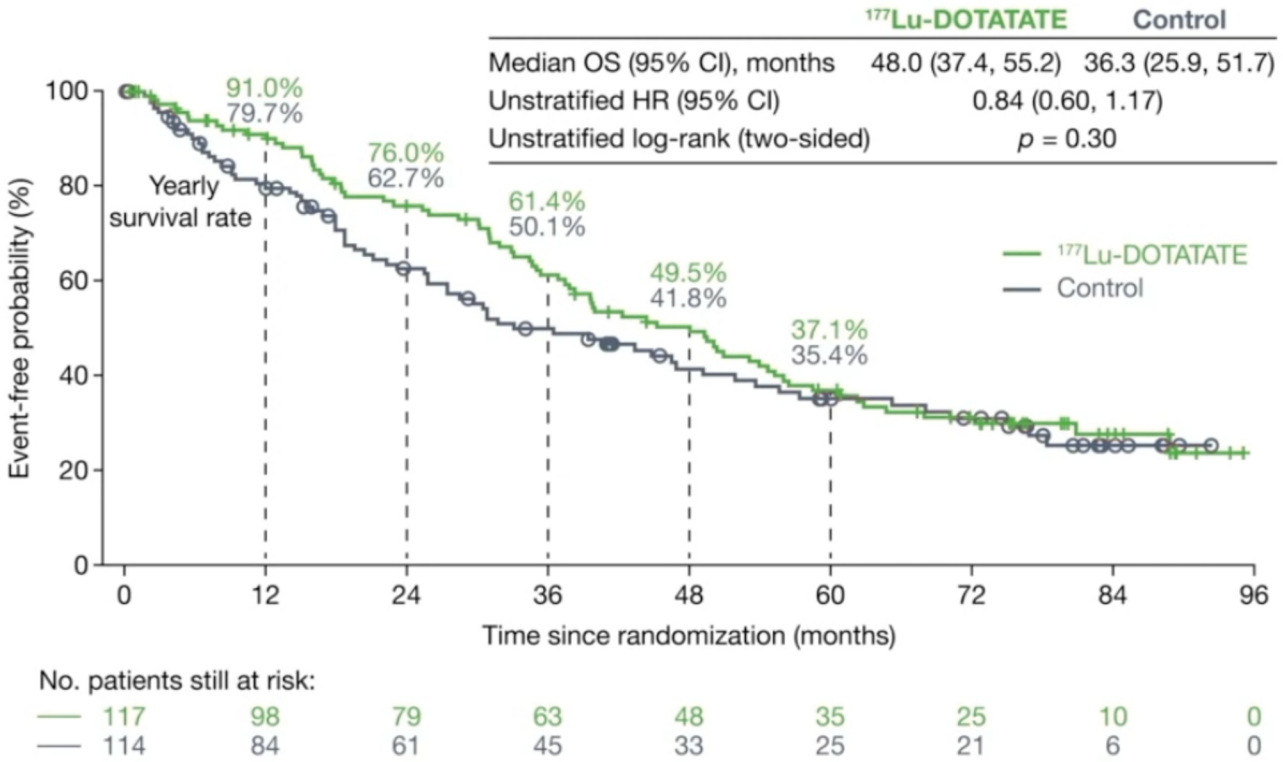
*After centrally confirmed disease progression, discontinuing study treatment without confirmed progression or completion of the 18-month treatment period (regardless of progression after the primary PFS analysis) patients entered long-term follow-up and could receive further anti-cancer treatments; †Long-acting octreotide 30 mg was administered Q8W during 177 Lu-DOTATATE treatment; ‡Controlled for type I error within a hierarchical testing procedure. DoR, duration of response; HRQoL, health-related quality of life; GBq, giga-becquerel; mCi, millicurie; ORR, objective response rate; OS, overall survival, PFS, progression-free survival, PFS2, time to second progression or death; Q3W, every 3 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks; RECIST, response evaluation criteria in solid tumors; TTP, time to progression.

- Objectif principal largement atteint :
  mPFS : NR « radiothérapie métabolique »
  vs 8, 4 mois dans le bras Octreotide seul .
(HR : 0,21 [0,13-0,33], p < 0,0001).
- Le taux de réponse est en faveur du bras RIV : 19 vs 3%.

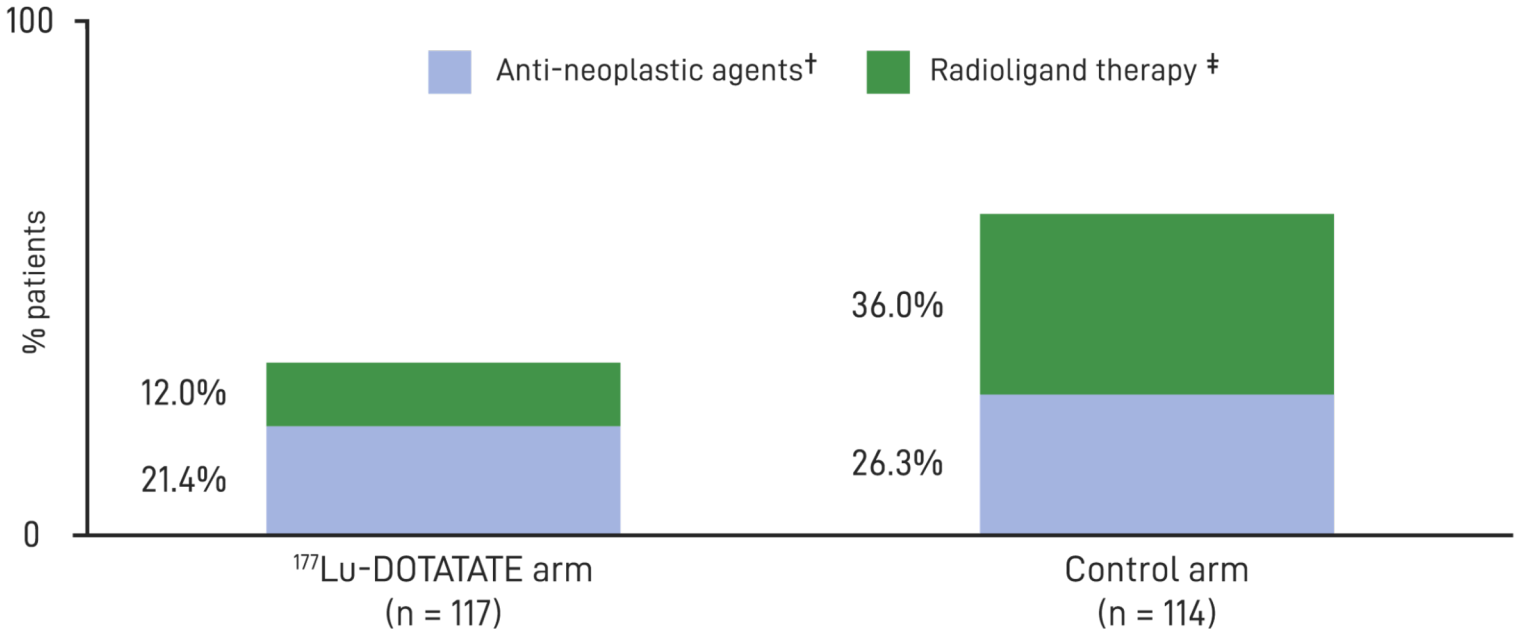
Jonathan R. Strosberg, NEJM 2017

O-2: Jonathan R. Strosberg, ESMO-GI 2021

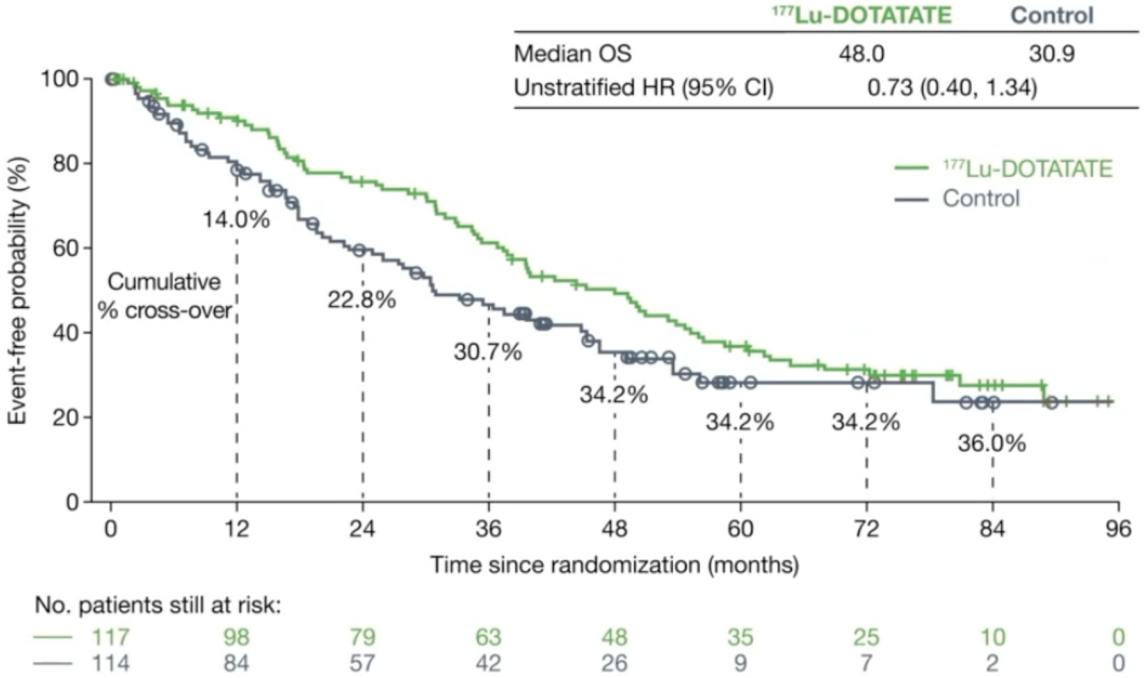
NETTER-1: Survie globale, population en ITT



Subsquent systemic anti-cancer treatments during long-term follow-up



NETTER-1: Survie Globale en prenant compte le cross-over dans le bras contrôle (RPSFT méthode)



- Survie globale non statistiquement différente

➔ MAIS

  - Ne remet pas en cause la positivité de l'étude
  - 36% de cross over (41/114) pdt le suivi
  - Amélioration de **11 mois** de l'OS avec la RIV

- Tolérance :

➔ 2 cas de L.A ou SMD (1,8%),

➔ taux identique EI G3 néphrotoxiques

CI, confidence interval; HR, hazard ratio; OS, overall survival; RPSFT, rank-preserving structural failure time.

FRÉQUENCE MÉDICALE ONCOLOGIE

2021

FRÉQUENCE MÉDICALE ONCOLOGIE

CANCERS COLORECTAUX MÉTASTATIQUES

- Mutations KRAS G12C
- CCRM dMMR/MSI-H
- CCRM BRAF V600E

Mutation KRAS G12C ?

Au niveau du gène → changement de nucléotide (G>T guanine remplacée par une thymine) en position c34

Au niveau protéique → changement d'acide aminé (glycine remplacée par cystéine) en position 12

Des inhibiteurs sont en cours d'évaluation pour les tumeurs mutées KRAS G12C. Le sotorasib® a été approuvé récemment par la FDA dans les cancers bronchiques KRAS G12C prétraités.

Dans les CCRM, plusieurs études rétrospectives suggèrent un pronostic péjoratif.

Schirripa M, et al. Clin Colorectal Cancer 2020

Ottaiano A, et al. Cancers (Basel) 2020

Henry JT et al JCO Precis Oncol 2021

Prévalence des mutations KRAS G12C et cancers digestifs

Abstract O-3: Characterization of KRAS mutation variants and prevalence of KRAS-G12C in gastrointestinal malignancies. M. Salem at al.

Etude rétrospective portant sur **17 009 patients avec un cancer digestif** (majorité de cancers colorectaux (CCR) et pancréatiques (CP))

Tumeurs mutées KRAS : N = 7 559

Tumeurs mutées KRAS G12C : **N= 325** (=1,9 % du total/4,3% des mutés KRAS)

Dans les CCR : association **KRAS G12C** et **tabagisme actif/sevré** (90% vs 45%)

Dans les CP : association **KRAS G12C** et **genre féminin** (86% vs 48%)

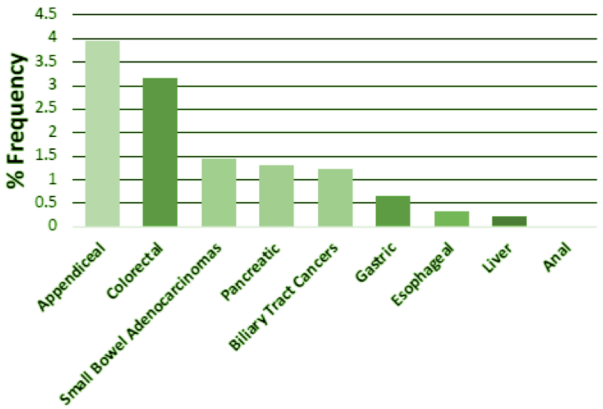
KRAS G12C associées avec

Mutations APC (67.1%), CDKN2A (9.2%), CTNNB1 (8.6%), KEAP1 (4.0%) et KMT2D (8.0%)

Charge mutationnelle élevée (TMB≥10 Mut/Mb)

Prévalence des mutations KRAS G12C et cancers digestifs

Abstract O-3: Characterization of KRAS mutation variants and prevalence of KRAS-G12C in gastrointestinal malignancies. M. Salem at al.



- Prévalence la plus importante dans les **carcinomes appendiculaires (3,9%), les cancers colorectaux (3,2%)**, de l'intestin grêle (1,4%), du pancréas et des voies biliaires (1,2%)
- **Pas de mutation KRAS G12C retrouvées dans les carcinomes épidermoïdes du canal anal** (0% vs 4,1%; N=195)
- **KRAS G12D et G12V** sont les plus fréquentes dans les cancers digestifs.

Mutations KRAS G12C et cancer colorectal

Abstract SO-13: KRAS-G12C mutations in a Nordic cohort of 1441 metastatic colorectal cancer patients. E.Österlund et al.

1 441 CCRM génotypés RAS et BRAF

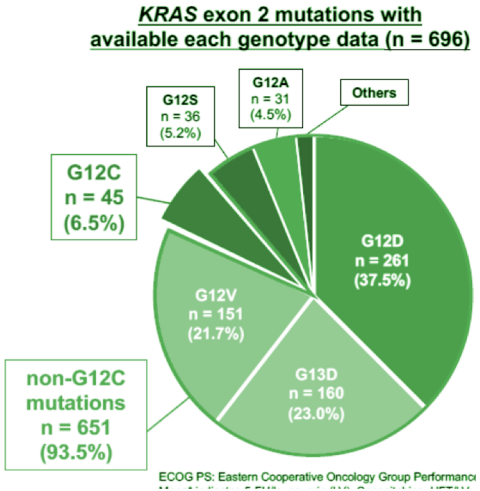
91 tumeurs KRAS G12C (6% de la population globale; 12% des KRASmt)

En comparaison aux autres mutations KRAS, les CCRM KRAS G12C :

- Sont plutôt localisés à G (NS)
- Ont moins de métastases péritonéales et plus de métastases pulmonaires (NS)
- Etaient plus souvent opérés de leurs métastases.

Mutations KRAS G12C et cancer colorectal

Abstract SO-14: The prognostic impact of KRAS G12C mutation in patients with metastatic colorectal cancer: a multicenter retrospective observational study. Y. Matsubara et al.



- Etude rétrospective
- KRAS exon 2 génotypé : N=696
  - KRAS G12C mutation : **n = 45**
- Pas de différence clinique selon type mutation
- OS/PFS significativement diminuées si KRASG12C

Mutations KRAS G12C et cancer colorectal

Discussion abstracts Pierre Laurent-Puig

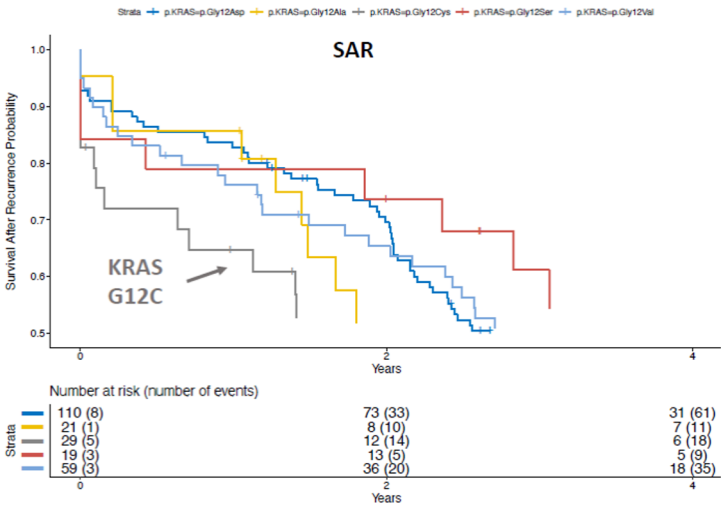
KRAS G12C et CCR stades II/III (études IDEA/PETACC8)

KRAS G12C = **12%***

Pas de différence en DFS ou OS

En revanche **la durée de survie après rechute est réduite**

* 92KRAS G12C/779 KRAS exon 2



Mutations KRAS G12C et cancer colorectal
Conclusion

• **Ces études confirment l'impact péjoratif des mutations KRAS G12C dans les CCR en situation métastatique** mais pas dans les stades II/III.

• Ces mutations sont associées avec une charge mutationnelle élevée et d'autres mutations.

Perspectives intéressantes d'association des inhibiteurs de KRAS G12C avec des inhibiteurs de checkpoint immunitaires.

Impact sur la résistance aux inhibiteurs spécifiques ?

• Des études cliniques sont en cours dans les CCRM KRAS G12C avec des inhibiteurs spécifiques (sotorasib, adagrasib...)

• Il faut être attentif aux mutations **KRAS G12C** dans les **adénocarcinomes coliques** mais aussi **appendiculaires** et de **l'intestin grêle**.

FRÉQUENCE MÉDICALE ONCOLOGIE

CANCERS COLORECTAUX MÉTASTATIQUES

CCRM dMMR/MSI-H - KN177

CCRM dMMR/MSI-H - **KN177**

Abstract O-8: Final Overall Survival for the Phase 3 KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer. T. André et al.

Etude de phase 3 déjà présentée à l'ASCO 2020, ASCO GI 2021 et publiée*

Pembrolizumab (P) vs chimiothérapie (C) en 1ère ligne métastatique

PFS médiane = 16.5 (P) vs 8.2 (C) mois; HR 0.60; P=0.00023

Effets indésirables de grade ≥3 moins fréquents avec P (22% vs 66%)

Meilleure qualité de vie avec P

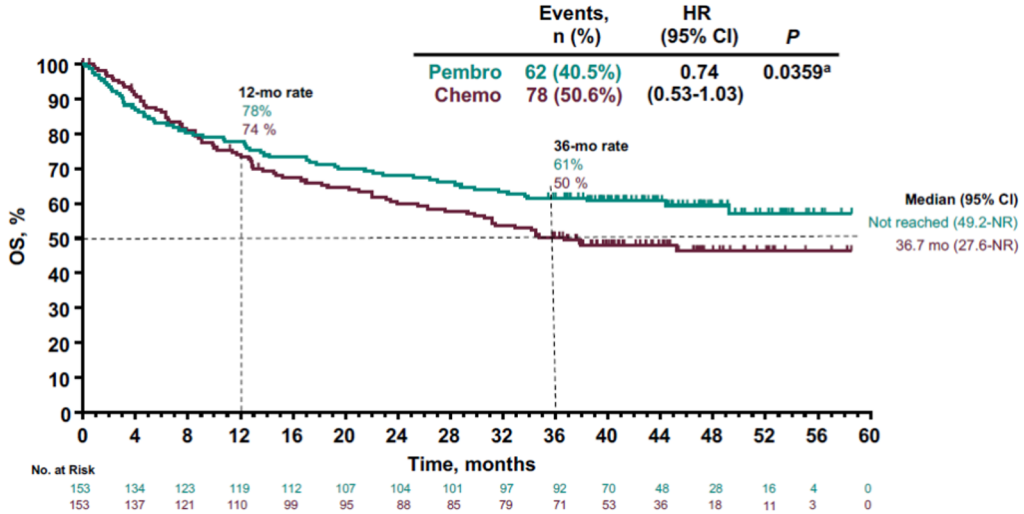
Accord FDA/EMA pour le pembrolizumab pour le traitement de 1ère ligne des patients avec CCR métastatique dMMR/MSI-H.

André T et al N Engl J Med. 2020 Dec 3;383(23):2207-2218.
André T et al Lancet Oncol. 2021 May;22(5):665-677.

CCRM dMMR/MSI-H - **KN177**

Abstract O-8: Final Overall Survival for the Phase 3 KN177 Study: Pembrolizumab Versus Chemotherapy in Microsatellite Instability-High/Mismatch Repair Deficient Metastatic Colorectal Cancer. T. André et al.

- Pas d'amélioration significative de la survie globale avec P
- Explication possible : cross-over (60% des pts) ?
- Analyse RPSFT : HR=0.66 (IC95% 0.42-1.04)



CCRM dMMR/MSI-H - **CM142**

Abstract SO-27: Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 4-year follow-up from CheckMate 142. T. André et al.

- Etude de phase II déjà présentée et publiée*
- Actualisation données efficacité/tolérance à 4 ans de suivi dans la cohorte **nivolumab (3 mg/kg) + ipilimumab (1 mg/kg)**
- **N= 119 pts** avec CCRM dMMR/MSI-H en 2ème ligne

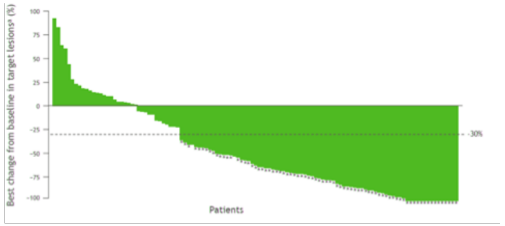
** Overman MJ. et al, J Clin Oncol. 2018 Mar 10;36(8):773-779.*
Overman MJ. et al, Lancet Oncol. 2017 Sep;18(9):1182-1191.

CCRM dMMR/MSI-H - **CM142**

Abstract SO-27: Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 4-year follow-up from CheckMate 142. T. André et al.

Outcome[a]	NIVO3 + IPI1 2L+ (N = 119)		
	13.4-month follow-up[1,b]	25.4-month follow-up[2,b]	50.9-month follow-up[b]
ORR,[c] n (%) 95% CI, %	65 (55) 45-64	69 (58) 49-67	77 (65) 55-73
Best overall response, n (%)			
CR	4 (3)	7 (6)	15 (13)
PR	61 (51)	62 (52)	62 (52)
SD	37 (31)	33 (28)	25 (21)
PD	14 (12)	14 (12)	14 (12)
Unable to determine	3 (3)	3 (3)	3 (3)
Disease control, n (%)[d] 95% CI, %	95 (80) 72-87	96 (81) 72-87	96 (81) 72-87
Median TTR (range), months	2.8 (1.1-14.0)	2.8 (1.1-24.4)	2.8 (1.1-37.1)
Median DOR (range), months	NR (NE)	NR (1.4+ to 32.5+)	NR (1.4+ to 58.0+)

- Il existe des réponses tardives à l'immunothérapie
- La durée médiane de réponse n'est pas atteinte



* 6 pts étaient en fait pMMR/MSS (taux de progression réel = 6%)

CCRM dMMR/MSI-H - **CM142**

Abstract SO-27: Nivolumab plus low-dose ipilimumab in previously treated patients with microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC): 4-year follow-up from CheckMate 142. T. André et al.

- PFS et OS médianes sont toujours non atteintes (taux à 48 mois 53% et 70,5%)
- La réponse au traitement ne varie pas dans les sous-groupes évalués (âge, sexe, ECOG PS, statut mutationnel BRAF/KRAS)
- La majorité des effets indésirables (EI) étaient de grade 1-2, comme déjà décrits.
- 13% des pts ont arrêté le traitement pour des EI reliés au traitement.

CCRM dMMR/MSI-H **- Conclusion**

L'immunothérapie a changé radicalement la prise en charge des CCR dMMR/MSI

- L'analyse du statut microsatellitaire est nécessaire chez tous les patients avec CCRM dès la 1ère ligne
- Le pembrolizumab a démontré son efficacité en 1ère ligne en réponse et PFS et une meilleure tolérance que la chimiothérapie.
- Les résultats des l'étude BMS CA 209-8HW nous permettront de savoir si une bi-immunothérapie fait mieux qu'une mono-immuno et si la tolérance est acceptable.
- Certains patients avec CCRM dMMR/MSI présentent une résistance primaire à l'immunothérapie et il faut adresser cette question par des études de recherche fondamentales et cliniques.

CCRM BRAF V600E – ANCHOR

Abstract O-10: ANCHOR CRC: Results from a single-arm, phase 2 study of encorafenib, binimetinib plus cetuximab in previously untreated BRAF V600E–mutant metastatic colorectal cancer. E. Van Cutsem et al.

Etude de phase II CCRM BRAF V600E en 1ère ligne (N=95)

Encorafenib, binimetinib + cetuximab

Objectif Pal : ORR (évalué par investigateurs)

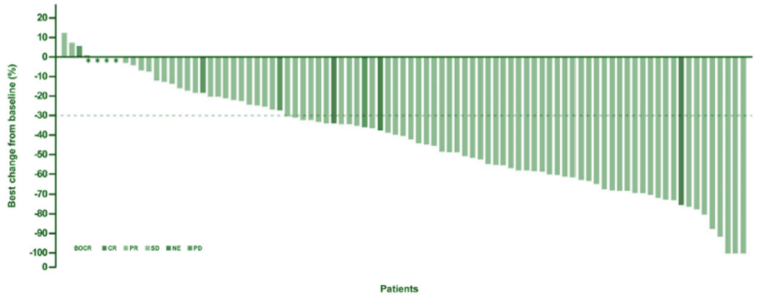
Demographic and disease characteristics

		Encorafenib + binimetinib + cetuximab (N=95), n (%)
Stage IV at study entry		95 (100)
BRAF^{V600E} mutation centrally confirmed		92 (96.8)
Female		51 (53.7)
Age, median (range), years <65 years / 65-74 years/ ≥75 years		65 (30–84) 43 (45.3) / 40 (42.1) / 12 (12.6)
Eastern Cooperative Oncology Group performance status (PS)	PS=0 PS=1	43 (45.3) 52 (54.7)
Location of primary tumor	Right side/transverse Left side (including rectum)	57 (60.0) 37 (38.9)
Time since initial diagnosis, median (range), days		66 (19—3235)
Number of metastatic organs	1 ≥2	23 (24.2) 72 (75.8)
Metastatic site locations	Liver Lymph node Peritoneum/omentum Lung	52 (54.7) 49 (51.6) 46 (48.4) 35 (36.8)
Liver metastasis only		7 (7.4)
Prior systemic therapy adjuvant / neoadjuvant / locally advanced		18 (18.9) 17 (17.9) / 3 (3.2) / 2 (2.1)

CCRM BRAF V600E – ANCHOR

Best percentage change in tumor measurements

Investigator's assessment, patients evaluable for efficacy (N=92#)



Critère principal de jugement = taux de réponse (cORR)

Investigator's assessment	Patients (N=92#), n (%)
cORR	**44 (47.8)**
95% CI	**37.3—58.5**
Best overall confirmed response	
CR	0
PR	44 (47.8)
SD	37 (40.2)
PD	5 (5.4)
Not evaluable	6* (6.5)

DCR = 88%

Suivi median = 14.4 mois
mPFS = 5.8 mois (IC95% 4.6—6.4)
mOS = 17,2 mois (IC95% 14.1—21.1)

Tolérance
- 99% EI (diarrhées, nausées, rash acnéiforme)
- 24% d'arrêts d'au moins un des traitements

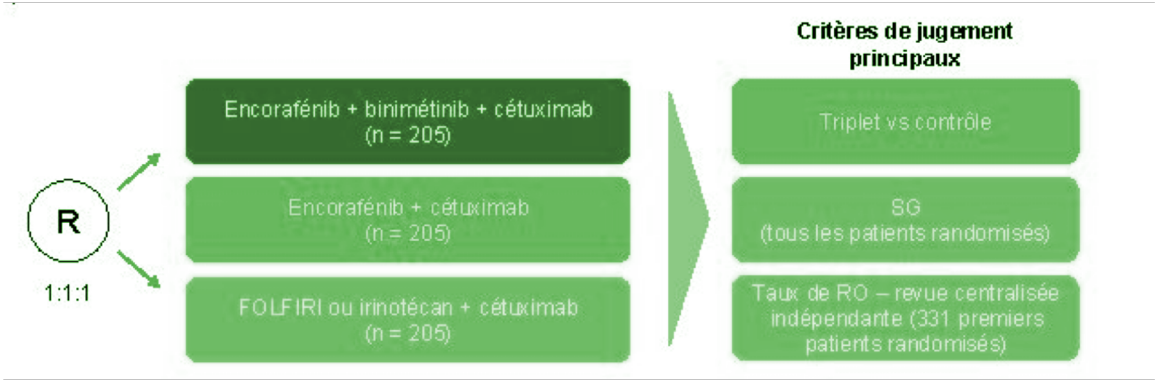
CCRM BRAF V600E – BEACON

Abstract SO-28: Effect of prior bevacizumab treatment in BRAF V600E-mutant metastatic colorectal cancer: overall survival with encorafenib + cetuximab +/- binimetinib in BEACON CRC. D. Aderka et al.

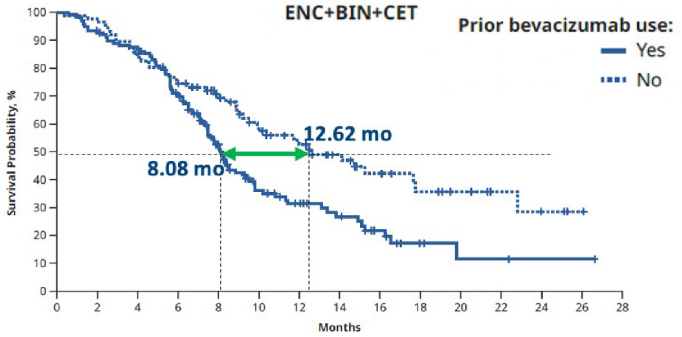
Analyse post-hoc de l'étude BEACON évaluant l'impact d'un traitement préalable par bevacizumab sur l'éfficacité de la combinaison cetuximab+encorafenib

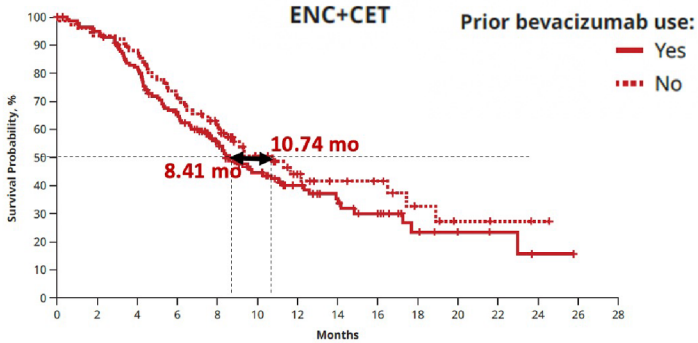
Design (ph IIIR)

- CCRM BRAF V600E
- ECOG-PS 0-1
- Progression sous chimio (1 ou 2 lignes ant.)
- Pas d'antiEGFR



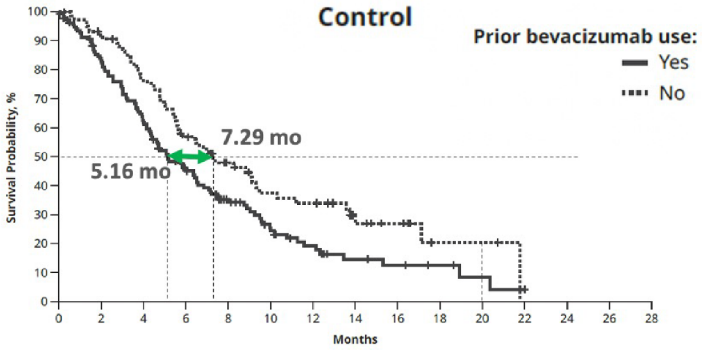
CCRM BRAF V600E – BEACON





Dans le bras doublet : pas de différence significative
(median 8.41 vs 10.74 months; HR 1.24 [95% CI 0.86–1.78])

Dans le bras encorafenib + binimetinib + cetuximab : **Survie globale plus courte chez les pts ayant déjà reçu du bevacizumab** (médiane 8,08 vs 12,62 mois ; HR 1,73 [IC95 % 1,21-2,49])

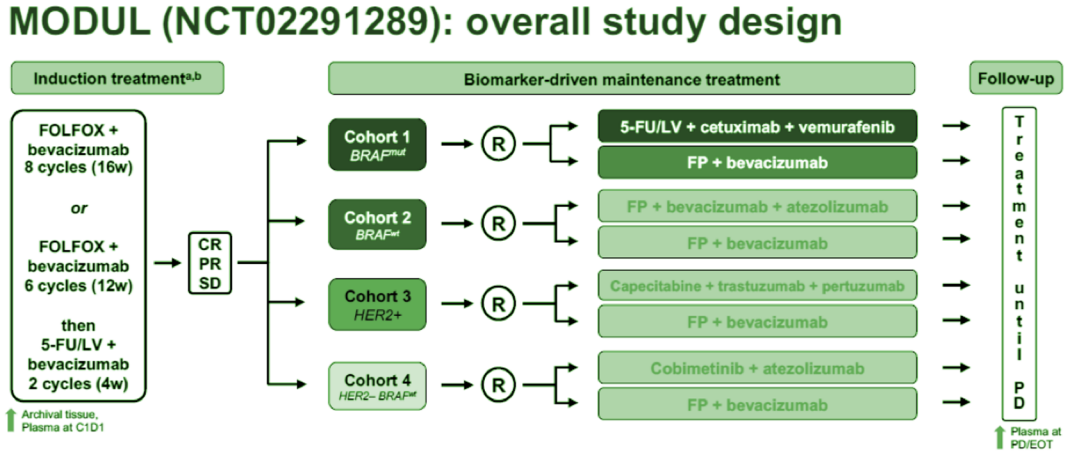


Dans le bras contrôle : survie prolongée si bev. antérieur
(median 5.16 vs 7.29 months; HR 1.52 [95% CI 1.09–2.13])

CCRM BRAF V600E – MODUL

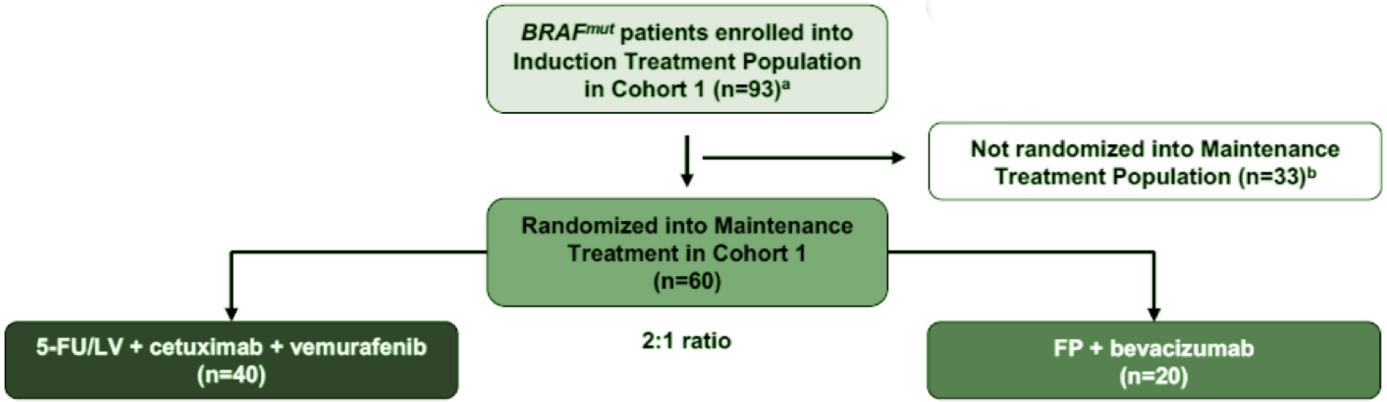
Abstract O-9: 5-FU/LV + cetuximab + vemurafenib as maintenance therapy for BRAF-mutant (BRAFmut) metastatic colorectal cancer (mCRC): Efficacy, safety, and exploratory biomarker findings from Cohort 1 of the MODUL trial. M. Ducreux et al.

- Etude de phase II
- Pts avec CCRM traités par FOLFOX-BEV puis randomisés entre allègement (5FU-BEV) vs traitement d'entretien expérimental bioguidé.
- Cohorte 1 = BRAF V600E
- Objectif P^{al} = PFS



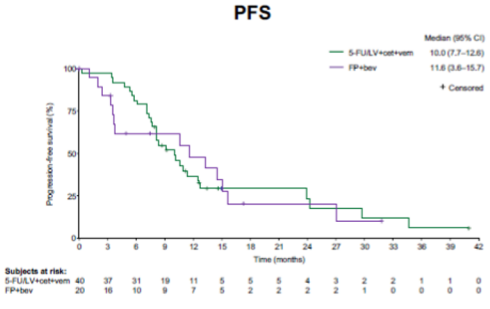
CCRM BRAF V600E – MODUL

Abstract O-9: 5-FU/LV + cetuximab + vemurafenib as maintenance therapy for BRAF-mutant (BRAFmut) metastatic colorectal cancer (mCRC): Efficacy, safety, and exploratory biomarker findings from Cohort 1 of the MODUL trial. M. Ducreux et al.

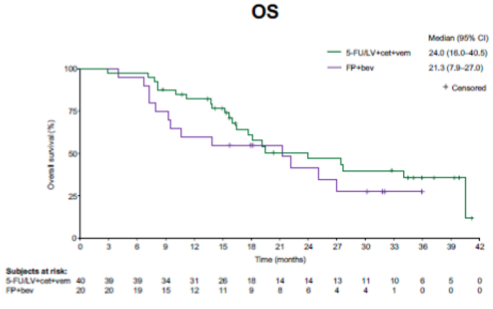


CCRM BRAF V600E – MODUL

Abstract O-9: 5-FU/LV + cetuximab + vemurafenib as maintenance therapy for BRAF-mutant (BRAFmut) metastatic colorectal cancer (mCRC): Efficacy, safety, and exploratory biomarker findings from Cohort 1 of the MODUL trial. M. Ducreux et al.



	5-FU/LV + cet + vem	FP + bev
Median PFS, months	10.0	11.6
Stratified HR (95% CI)	0.95 (0.50–1.82) p=0.87	



	5-FU/LV + cet + vem	FP + bev
Median OS, months	24.0	21.3
Stratified HR (95% CI)	0.69 (0.34–1.38) p=0.29	

- mPFS et mOS similaires
- Taux de réponse plus favorable dans le bras expérimental : 50% vs. 25.0% (p=0.06)

- Les analyses ancillaires montrent que la pression sélective du traitement conduit à l'acquisition de mutations de la voie MAPK expliquant la résistance.

CCRM BRAF V600E – Conclusion

Pas de changement de pratique

- L'étude ANCHOR montre un taux de réponse de 48% avec encorafenib, binimetinib + cetuximab en 1ère ligne

Mais phase II non randomisée. Avenir au triplet en 1ère ligne ?

- L'analyse post-hoc de l'étude BEACON pose la question de l'impact négatif du bevacizumab reçu antérieurement sur l'éfficacité ultérieure du triplet.

Mais pas de différence dans le bras doublet (AMM)

- L'étude MODUL montre qu'il est possible de proposer un traitement de maintenance aux patients avec CCRM BRAF V600E sans avoir d'effet délétère sur la survie (mPFS 11,6 mois et mOS =21 mois dans le bras chimio allégée).

Les analyses ancillaires permettent d'expliquer les mécanismes de résistance acquises

FRÉQUENCE MÉDICALE ONCOLOGIE

2021

FRÉQUENCE MÉDICALE ONCOLOGIE

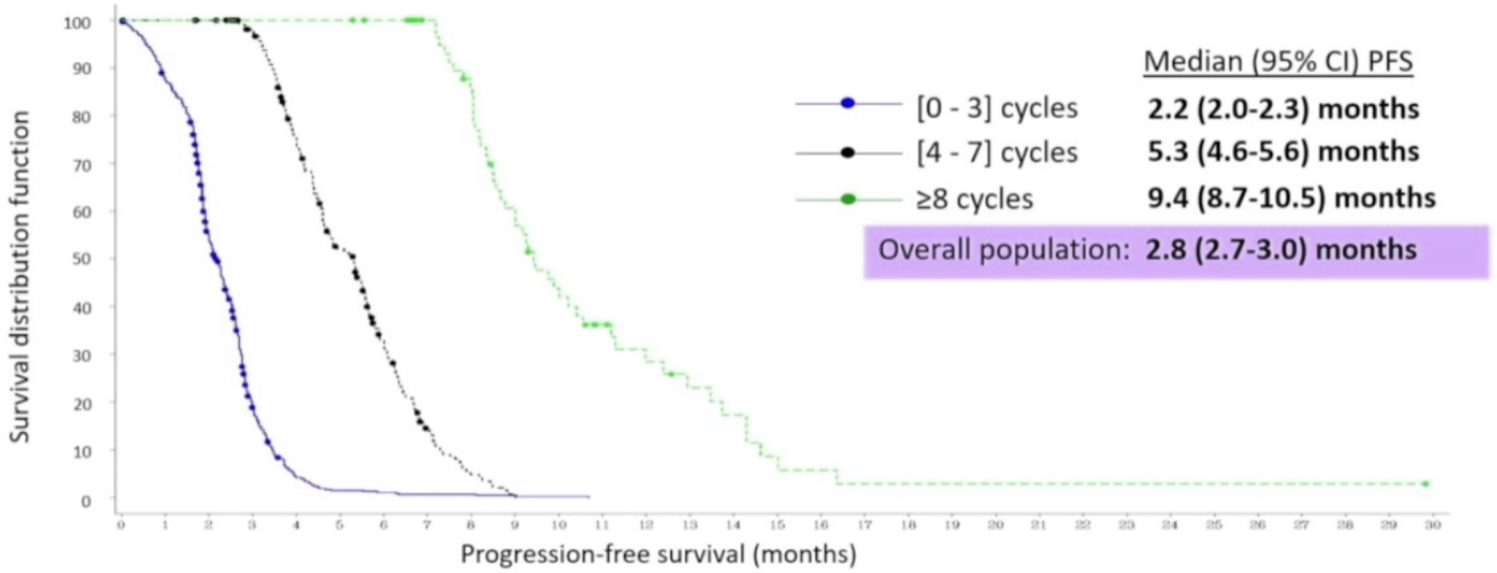
Cancer Colorectal

Traitement au delà de la 2ème ligne

PRECONNECT résultats finaux

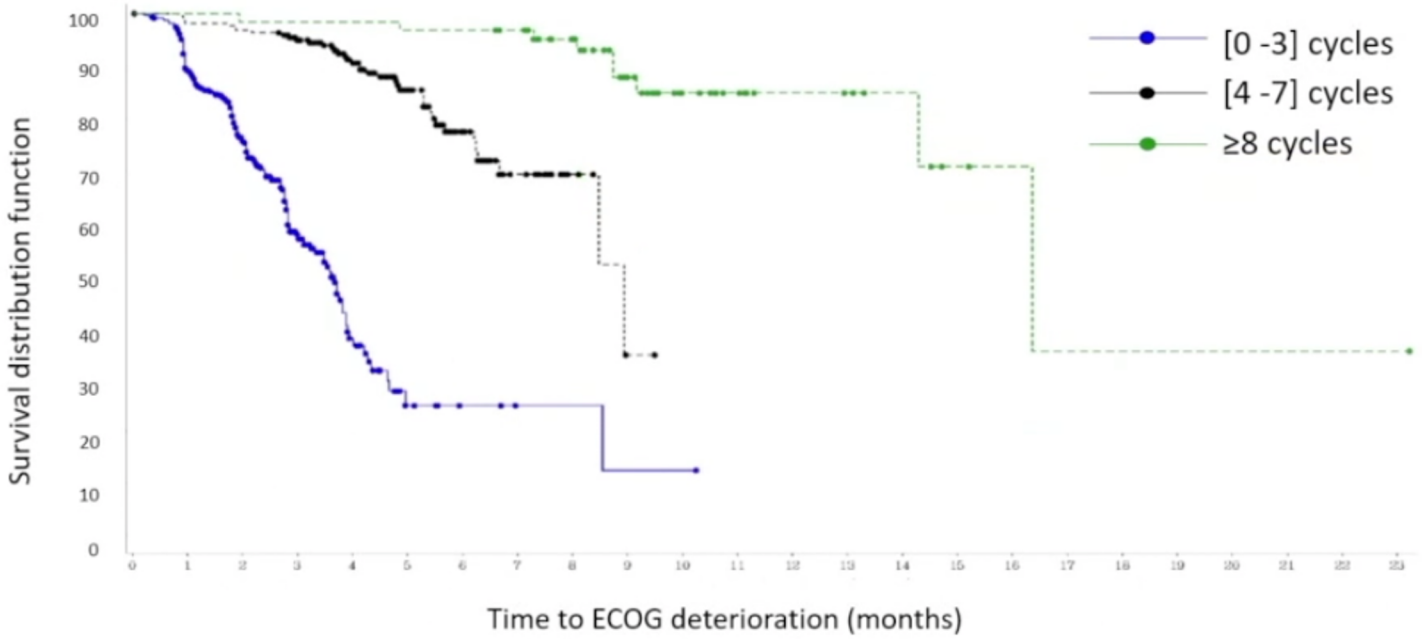
Pour rappel: phase 3b, 16 pays, 914 patients inclus, indication de l'AMM

Caractéristiques à baseline significativement corrélées à la durée de traitement : ECOG PS 0, délai ≥18 mois depuis diagnostic de métastases, statut RAS



Taieb J et al, SO-18

PRECONNECT résultats finaux



Median (95% CI) time to ECOG PS deterioration
3.6 (3.3-3.9) months
8.9 (8.5-NC) months
16.4 (14.3-NC) months

Taieb J et al, SO-18

Phase 2 WJOG8916G
rechallenge avec Trifluridine/Tipiracil + Cetuximab

Posologies usuelles de TTP et cetuximab
Objectif principal : taux de contrôle tumoral ; H1 > 65%

Characteristic	Categories	n (%)
Age, years	median (range)	60 (37-77)
Gender	male/female	33/23 (59/41)
ECOG PS	0/1	31/25 (55/45)
Location of primary lesion	right*/left†	5/51 (9/91)
Pathology	well, mode /por, muc, sig	51/5 (91/9)
No. of metastatic sites	0-1/≥ 2	17/39 (30/70)
Regorafenib use before protocol treatment	yes/no	11/45 (20/80)
Prior anti-EGFR antibody	monotherapy/combination	28/28 (50/50)
Best response of prior anti-EGFR antibody	PR/SD/PD/NE	34/12/7/3 (61/21/13/5)
	PR or long (≥6M) SD/short SD (<6M) or PD/NE	39/14/3 (70/25/5)
Duration of prior anti-EGFR antibody treatment	median (range)	8.5 M (1.6-44)
Anti-EGFR antibody-free interval‡	median (range)	3.9 M (0.49-46)

**cecum to transverse, † descending to rectum*
‡ Anti-EGFR therapy-free interval was defined as the period from the last administration date of prior anti-EGFR antibody to the enrollment date.

Masuishi T et al, SO-19

Phase 2 WJOG8916G
rechallenge avec Trifluridine/Tipiracil + Cetuximab

Taux de réponse objective : 3,6%
Taux de contrôle tumoral : 54%
SSP médiane : 2,4 mois (IC 95% : 2,1-3,7)
SG médiane : 9,8 mois (IC 95% : 7,4-12,2)

Adverse Events (AEs)

	All, n (%)	≥ G3, n (%)
Hematologic		
Neutropenia	41 (73)	31 (55)
Anemia	43 (77)	17 (30)
Platelet count decreased	32 (57)	5 (9)
Non-hematologic		
Dermatitis acneiform	42 (75)	4 (7)
Hypomagnesemia	42 (75)	9 (16)
Dry skin	33 (59)	3 (5)
Fatigue	30 (54)	1 (2)
Appetite loss	29 (52)	4 (7)

Analyses de sous-groupes

Factor		N	DCR (%) (95% CI)	*P*-value	mPFS (M) (95% CI)	*P*-value	mOS (M) (95% CI)	*P*-value
Location of primary lesion	Right	5	0 (0-52)	0.015	1.9 (1.6-2.1)	< 0.01	7.3 (3.9-12.7)	0.048
	Left	51	59 (44-72)		3.6 (2.1-3.8)		10.3 (8.1-13.0)	
Response to prior anti-EGFR antibody*	Short SD/PD	14	29 (8-58)	0.033	2.0 (1.5-3.6)	< 0.01	6.6 (3.9-14.2)	0.22
	Long SD/PR	39	62 (45-77)		3.7 (2.1-4.0)		10.9 (8.3-13.0)	
Anti-EGFR antibody-free interval	< 6 M	35	49 (31-66)	0.42	2.3 (2.0-3.7)	0.81	9.8 (7.3-12.7)	0.40
	≥ 6 M	21	62 (38-82)		3.6 (1.9-3.9)		10.7 (6.7-)	

*Long-term SD was defined as stable disease ≥ 6 months, Short-term SD was defined as stable disease < 6 months. Three patients with NE in prior anti-EGFR antibody were excluded.

Masuishi T et al, SO-19

Phase 2 WJOG8916G
rechallenge avec Trifluridine/Tipiracil + Cetuximab

Analyse ADNtc avant traitement n=53

Recherche mutations RAS, BRAF, PIK3CA et amplifications MET, HER2
- mutation RAS n=24 (45%), BRAF n=10 (19%) et PIK3CA n=7 (13%)
- amplification HER2 n=6 (11%), MET n=4 (8%)

Résultats selon :

- RAS muté	SSP 2,1 vs 3,8 mois (HR=2,6 ; p=0,0015)
	OS 8,9 vs 11,6 mois (HR=2,1 ; p=0,022)
- PIK3CA muté	SSP 1,9 vs 3,7 mois (HR=2,3 ; p=0,045)
	OS 5,4 vs 10,6 mois (HR=4,1 ; p=0,0014)

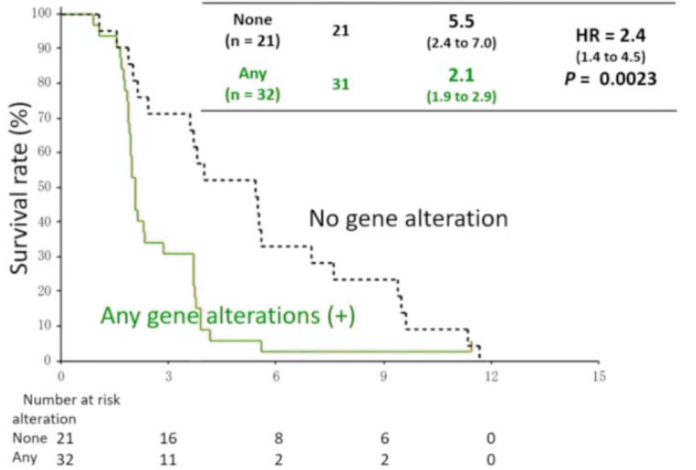
Takahashi N et al, O-6

Phase 2 WJOG8916G
rechallenge avec Trifluridine/Tipiracil + Cetuximab

Analyse ADNtc avant traitement – tous gènes confondus

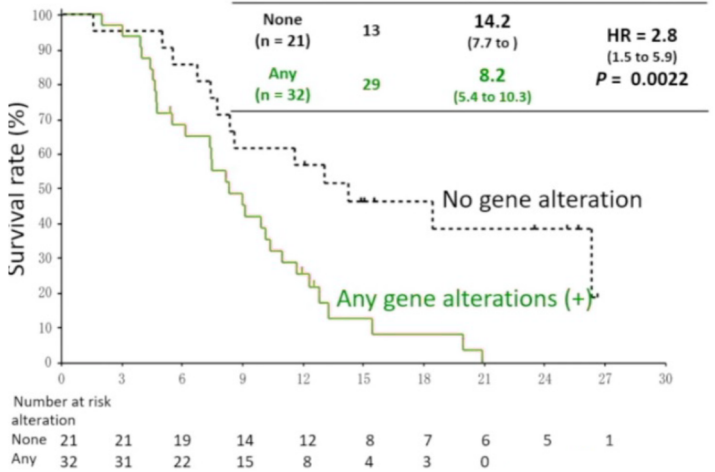
Survie sans progression

Gene Alterations	No. of events	Median PFS (M) (95% CI)	HR (95% CI) *P* value
None (n = 21)	21	5.5 (2.4 to 7.0)	HR = 2.4 (1.4 to 4.5)
Any (n = 32)	31	2.1 (1.9 to 2.9)	*P* = 0.0023



Survie globale

Gene Alterations	No. of events	Median OS (M) (95%CI)	HR (95% CI) *P* value
None (n = 21)	13	14.2 (7.7 to)	HR = 2.8 (1.5 to 5.9)
Any (n = 32)	29	8.2 (5.4 to 10.3)	*P* = 0.0022

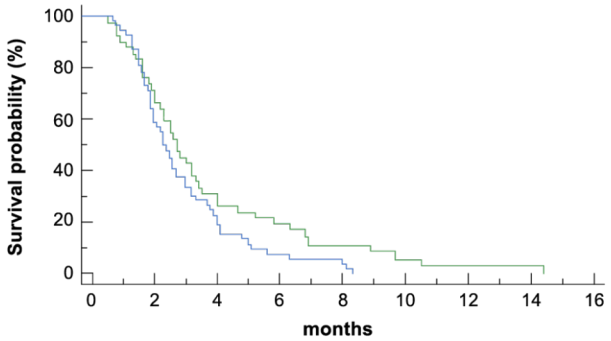


REGOLAND

100 patients traités par regorafenib
Evaluation prospective de l'Ang-2 et Tie-2 suite à une étude rétrospective (Antoniotti C et al, ASCO GI 2018)

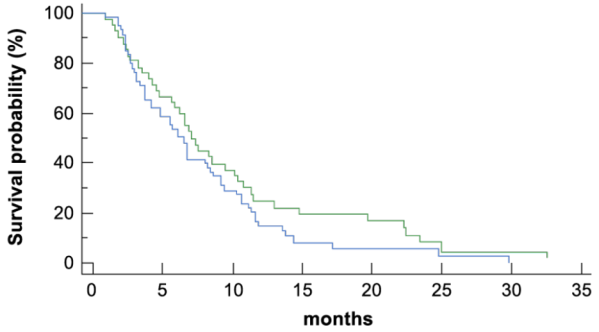
Objectif principal : évaluer si la modification du taux d'Ang-2 entre J1 et J15 est pronostique

Survie sans progression



Early decrease (n=58) mPFS 2.4 months
Early increase (n=42) mPFS 2.7 months
HR: 0.72 [95%CI: 0.48-1.08], log-rank *P*=0.095

Survie Global

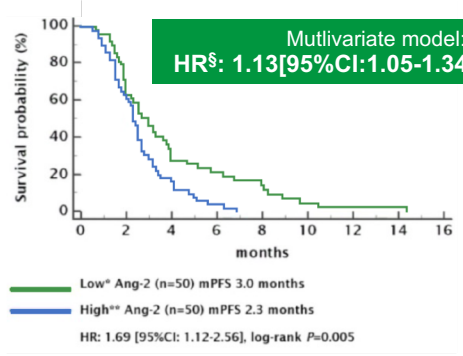


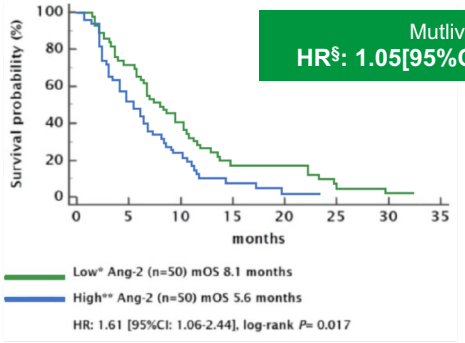
Early decrease (n=58) mOS 6.2 months
Early increase (n=42) mOS 7.0 months
HR: 0.77 [95%CI: 0.51-1.16], log-rank *P*=0.204

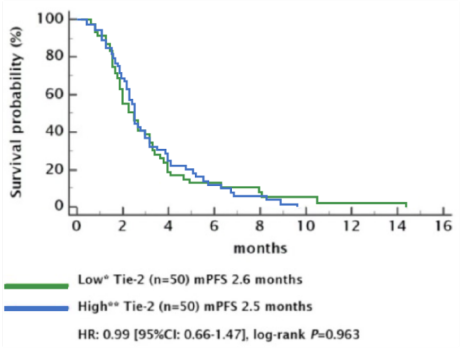
REGOLAND

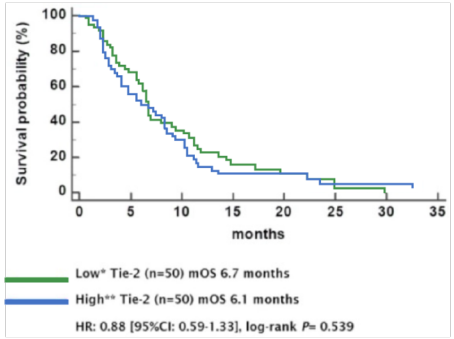
Objectifs secondaires : évaluer la valeur pronostique des taux d'Ang-2 et de Tie-2

	Survie sans progression	Survie globale
Ang-2	Mutlivariate model: **HR§: 1.13[95%CI:1.05-1.34], *P*=0.002**	Mutlivariate model: **HR§: 1.05[95%CI:0.96-1.15], *P*=0.273**
Tie-2		









Conclusion – Traitement ≥2ème ligne

- PRECONNECT : confirmation de l'efficacité du trifluridine/tipiracil, tolérance excellente sans dégradation du PS sous traitement

- WJOG8916G : étude négative mais sélection des patients sous optimale (réponse en 1ère ligne, délai entre 1ère administration de l'Ac anti-EGFR et rechallenge)
  Intérêt confirmé de l'ADNtc avant traitement

- REGOLAND : étude négative sur l'évolution de l'Ang-2 entre J1 et J15, valeur pronostique de l'Ang-2 confirmée

Cancer Colorectal

ADN tumoral circulant
(ADNtc)

ADNtc, ACE et Volume tumoral avant traitement

Etude ancillaire de l'étude de phase 2 randomisée VALENTINO (FOLFOX panitumumab 8 cycles puis randomisation entre deux bras de maintenance LV5FU2 panitumumab ou panitumumab seul)

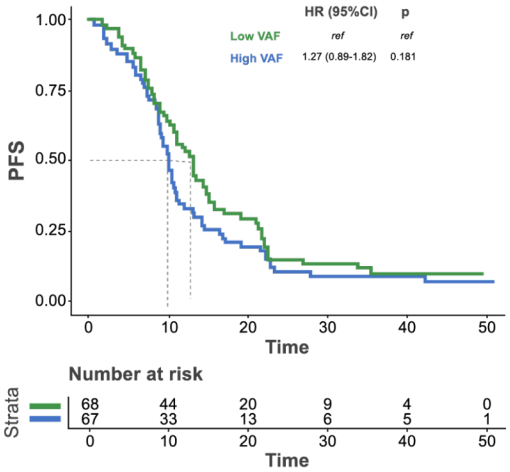
135 des 229 patients inclus avec prélèvement ADNtc à inclusion
Quantité d'ADNtc évaluée par la AF (« variant allelic fraction » = taux d'ADNtc)

Résultats
VAF significativement plus élevée en cas de métastases hépatiques (0,22 vs 0,01 ; p<0,001)
métastases synchrones (0,19 vs 0,01 ; p<0,001)

VAF significativement corrélée avec ACE (R2=0,061 ; p=0,003)
cibles RECIST (R2=0,116 ; p<0,001)

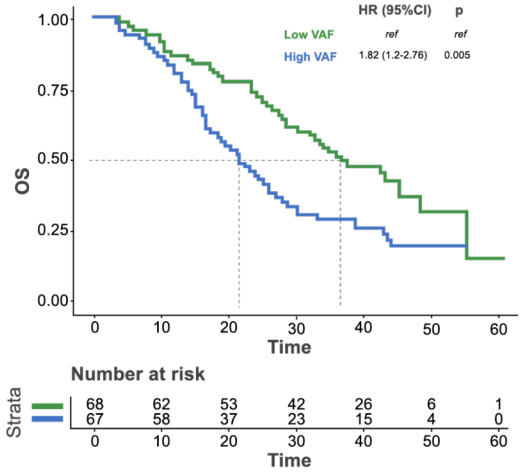
ADNtc, ACE et Volume tumoral avant traitement

Survie sans progression



mPFS: 9.9 vs 12.7 months

Survie globale



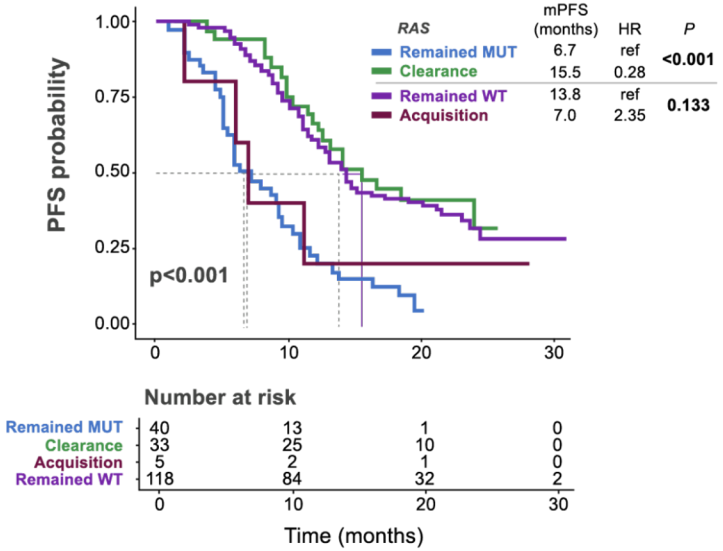
mOS: 21.8 vs 36.5 months

Features		HR (univariable)	HR (multivariable)
Age	<70	-	-
	≥70	1.09 (0.68-1.76, p=0.711)	-
Sex	Male	-	-
	Female	1.25 (0.82-1.91, p=0.304)	-
ECOG PS	0	-	-
	1	1.57 (1.01-2.43, **p=0.044**)	1.84 (1.15-2.96, **p=0.011**)
Adjuvant	No	-	-
	Yes	0.66 (0.33-1.33, p=0.249)	-
CEA - 139.1 vs 8.5 [ng/ml]		1.01 (0.99-1.02, p=0.334)	-
Target lesion size - 117.5 vs 50 [mm]		1.15 (0.94-1.42, p=0.174)	-
VAF - 45.2% vs 2%		**1.46 (1.06-2.01, p=0.022)**	**1.53 (1.09-2.13, p=0.013)**
No of metastatic sites	1	-	-
	>1	2.20 (1.45-3.33, **p<0.001**)	2.23 (1.44-3.44, **p<0.001**)
Sidedness	left	-	-
	right	2.17 (1.28-3.69, **p=0.004**)	2.60 (1.49-4.53, **p=0.001**)
Metastases timing	Synchronous	-	-
	Metachronous	0.60 (0.34-1.07, p=0.085)	0.65 (0.33-1.27, p=0.208)

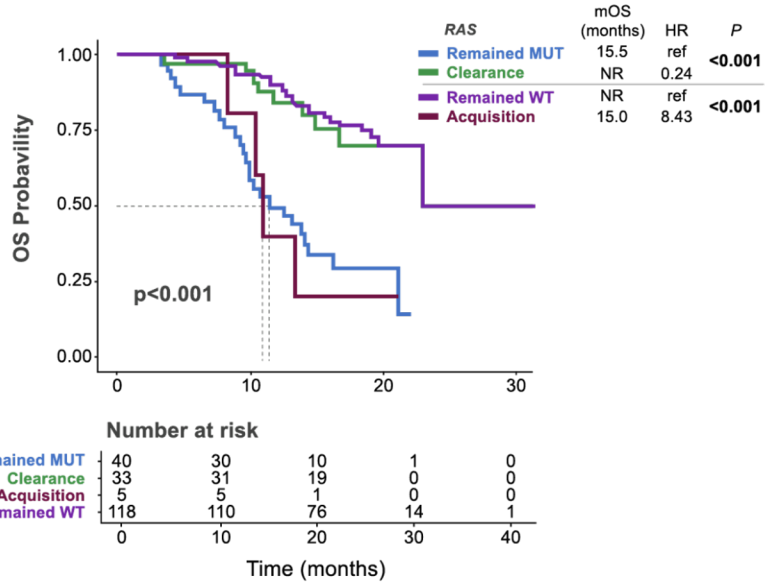
Evolution sous traitement

Cohorte prospective de 196 patients avec monitoring de ADNtc sous 1ère ligne

Survie sans progression



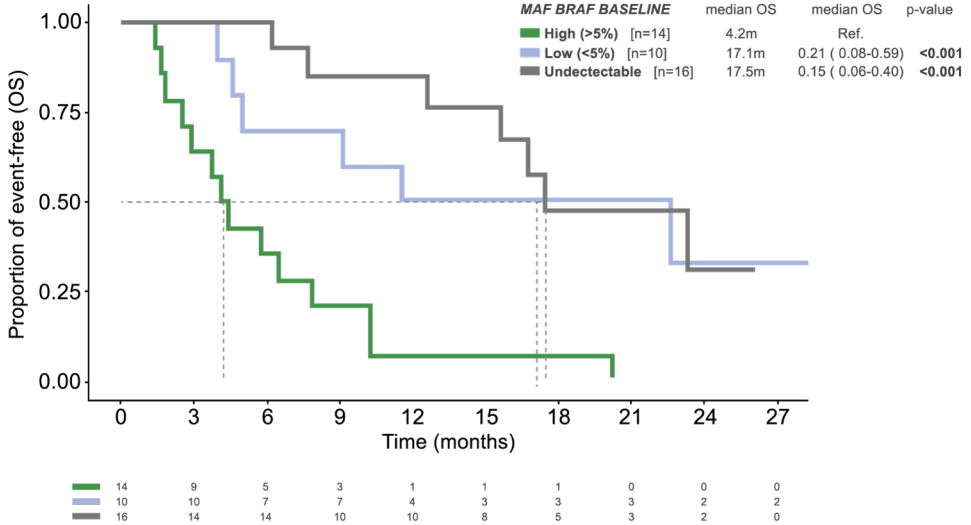
Survie globale



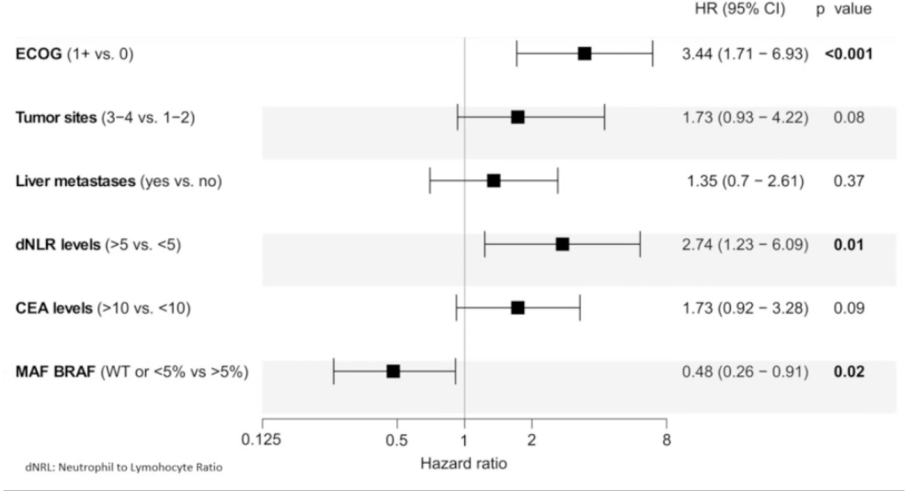
BRAF muté et ADNtc

Cohorte prospective de 86 patients traités par inhibiteurs de BRAF, anticorps anti-EGFR, +/- inhibteur de MEK en ≥2ème ligne
=> 40 patients avec ADNtc à inclusion

Survie globale

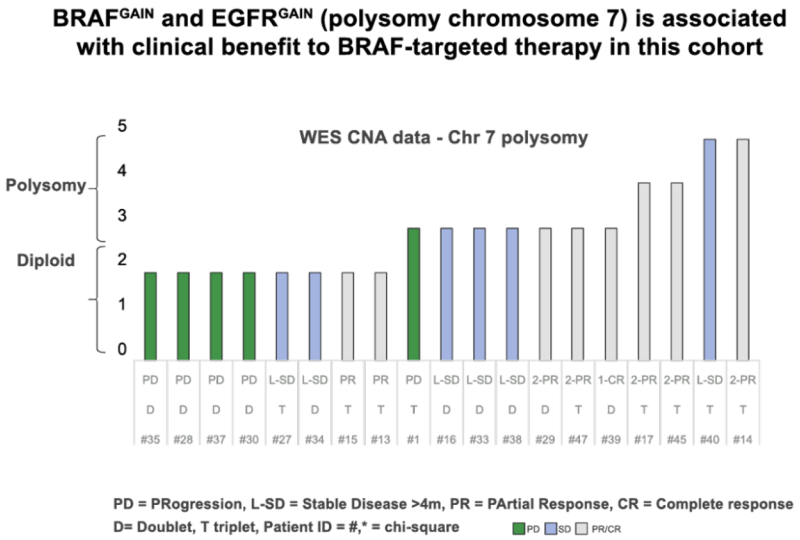


Overall Survival Multivariate Model

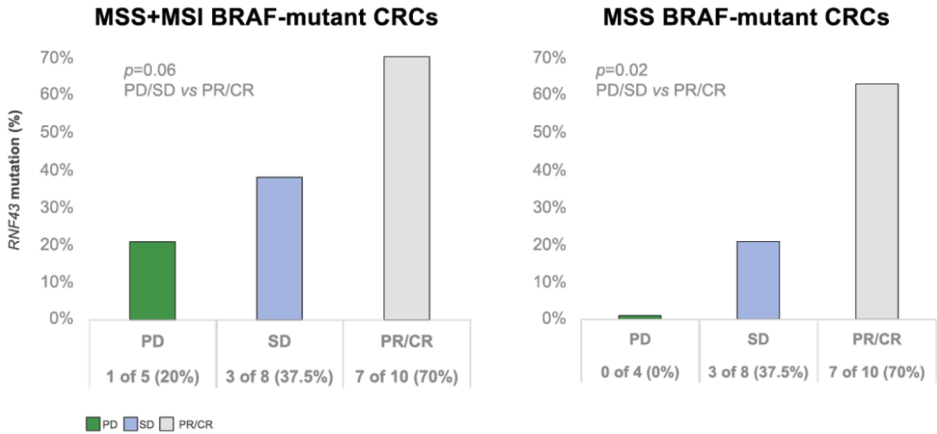


BRAF muté et anomalies associées ?

Cohorte prospective de 86 patients traités par inhibiteurs de BRAF, anticorps anti-EGFR, +/- inhibteur de MEK en ≥2ème ligne
=> 23 patients avec whole exome à partir du tissu



Mutations *RNF43*



Conclusion – ADNtc

- Le taux de VAF corrélé au taux d'ACE et aux cibles tumorales RECIST

=> Seuil à définir pour un score pronostique

- Évolution de l'ADNtc sous traitement pronostique de l'efficacité thérapeutique
- La détection et le taux de MAF sont pronostiques dans les cancers colorectaux BRAF mutés
- L'amplification du chromosome 7 et les mutations de RNF43 pourraient être prédictives de l'efficacité des doublet/triplet en 2ème ligne

FRÉQUENCE MÉDICALE ONCOLOGIE

2021